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JAMES YOUNG

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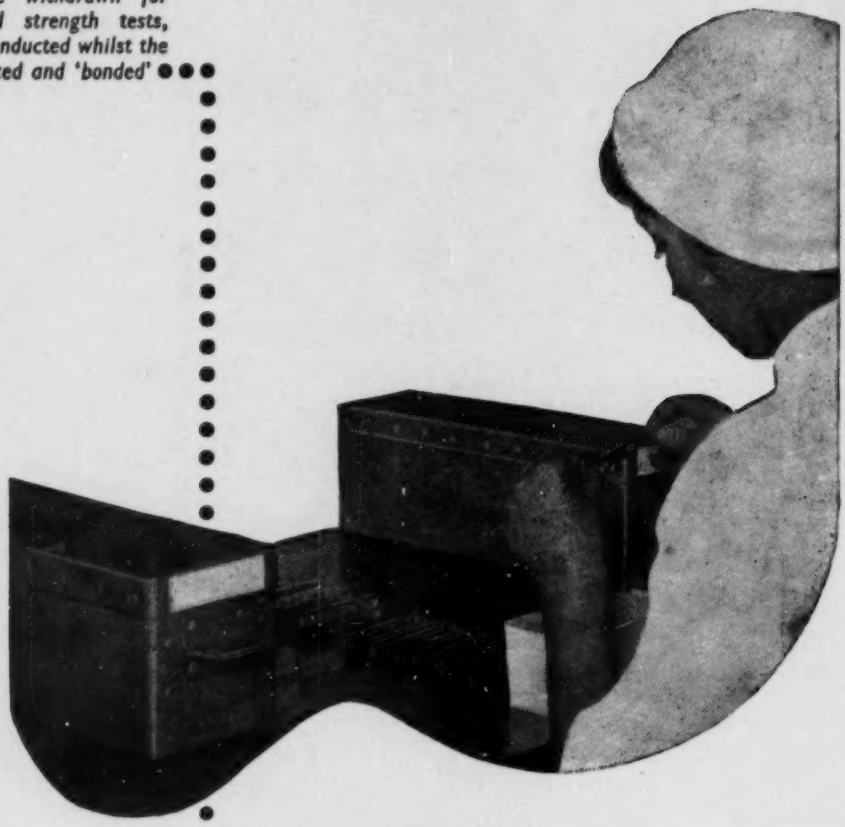

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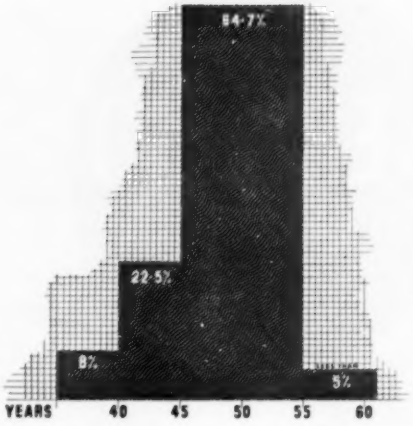

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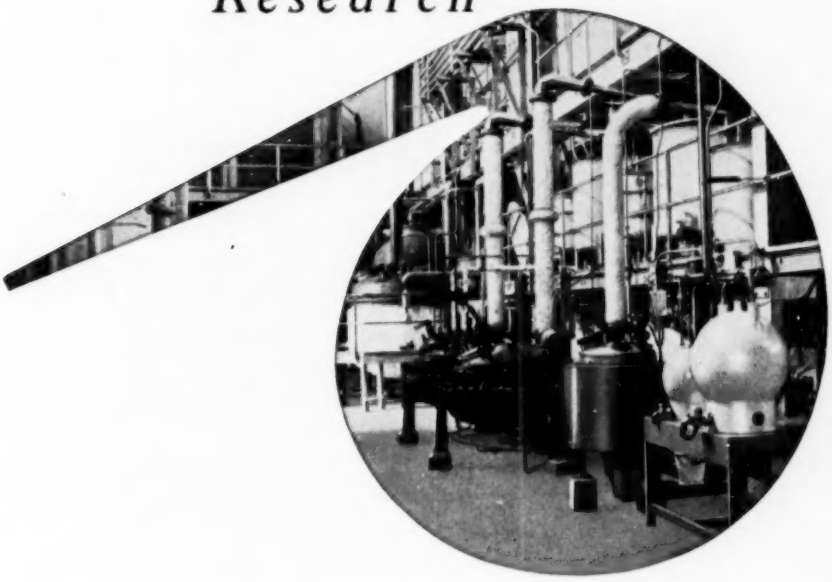

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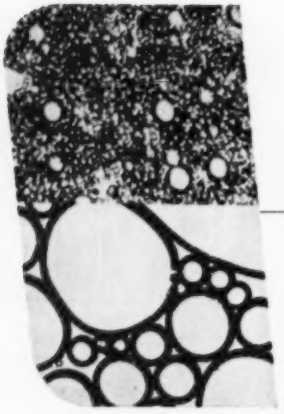

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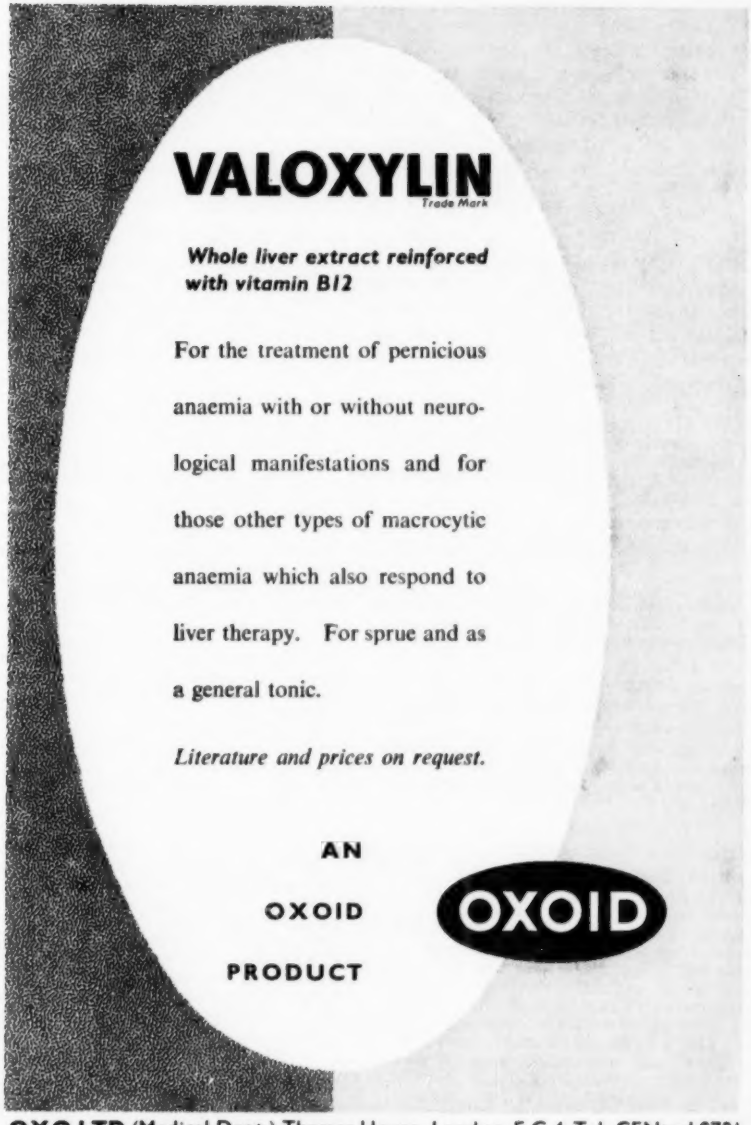
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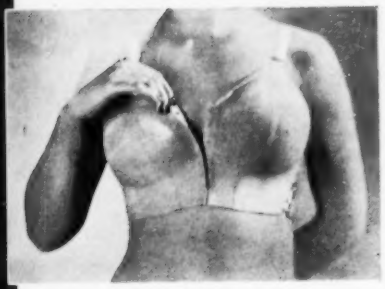

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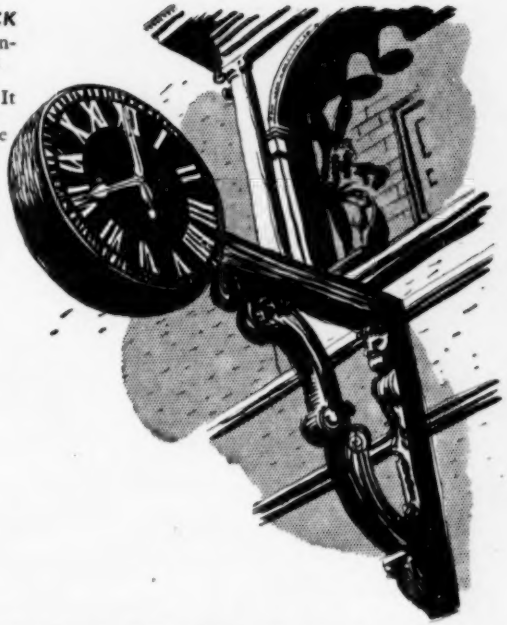

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FURTHER ANALYSIS OF CONTROLLED TRIALS* OF TREATMENT OF HAEMOLYTIC DISEASE OF THE NEWBORN

BY

P. ARMITAGE, Ph.D.,

AND

P. L. MOLLISON, M.D., M.R.C.P.

Medical Research Council's Statistical Research Unit, London School of Hygiene and Tropical Medicine, and Blood Transfusion Research Unit, Postgraduate Medical School of London

THE planning of the trials described in this report was first considered at a meeting held in London in November, 1948, at which seventeen centres from various parts of Great Britain and Ireland were represented. At that time there was much uncertainty about the merits of different methods of treatment of haemolytic disease of the newborn and this was reflected in wide differences between practice at the various centres. However, there were few people who felt confident that one method was definitely superior to another and it was thus possible to plan trials in which one form of treatment was alternated with another at each centre. It was originally hoped that exchange transfusion could be tried against simple transfusion and premature induction of labour against spontaneous delivery at term, one of the four possible combinations being selected for each case by a system of random numbers. However, only a few centres were willing to follow this plan. Some centres were prepared to use exchange transfusion and simple transfusion alternately and to pursue a fixed policy with regard to time of delivery; others agreed to use premature induction of labour and spontaneous delivery alternately and then to give either exchange transfusion to all infants or simple transfusion to all infants. It was a condition of taking part in the trials that at every centre at least two forms of treatment should be compared with one another for it was considered that only in this way could valid comparisons be made.

The trials were begun in August, 1949. After one year a disappointingly small number of cases had been collected; a preliminary analysis suggested that the different treatments under trial might all produce similar results. Thus, of 38 infants treated by simple transfusion, 5 had died and, of 33 infants treated by exchange transfusion, 4 had died. It was considered that these findings made it all the more important to continue the trials. An effort was therefore made to persuade other centres to take part for it was feared that unless the rate of collection of cases was considerably increased it might take years to demonstrate any differences.

* The trials of which results are described here were conducted at several different centres. More than half the infants were treated by Dr. W. Walker of the Children's Department, Royal Victoria Infirmary, Newcastle upon Tyne. Clinicians responsible for conducting the trials at other centres were: Professor J. C. McC. Browne and Dr. P. L. Mollison (Hammersmith); Dr. W. A. B. Campbell (Belfast); Dr. W. R. F. Collis and Dr. P. C. D. MacClancy (Rotunda); Miss Doreen Daley (St. Helier); Dr. R. J. Drummond and Dr. Beryl Bevan (Cardiff); Dr. D. M. T. Gairdner (Cambridge); Professor W. F. Gaisford (Manchester); Dr. John Murray (Queen Charlotte's); Mr. S. D. Perchard and Dr. V. W. Pugh (Mile End); Dr. Margaret M. Pickles (Oxford), and Dr. G. H. Tovey (Bristol). The scheme was organized by the Blood Transfusion Research Unit of the Medical Research Council, with assistance from the Council's Statistical Research Unit, and Dr. J. A. Fraser Roberts at the London School of Hygiene and Tropical Medicine.

During the second year the figures were frequently reviewed as the number of cases increased. Towards the end of August, 1951, it became clear that the mortality among premature infants treated by simple transfusion was higher than that of any other group. Accordingly the trials were stopped and subsequent analysis confirmed that significant differences had indeed been demonstrated. In view of the practical importance of the conclusions a preliminary report was published (Mollison and Walker, 1952). The present report gives a fuller account of the trials and includes various previously unpublished analyses. In addition it gives an account of follow-up studies on infants treated in the trials.

Methods

Selection of Cases

Women included in the trials were those whose serum was found to contain Rh antibody, the examination having been made not less than 30 days before the expected day of delivery. For the detection of Rh antibody one or both of the following tests was used: agglutination in albumin (or albumin-plasma) and the indirect antiglobulin test.

Women were not included if they were known to have diabetes mellitus or to be carrying more than one foetus, or if their serum gave a positive Wassermann reaction.

At some time after the thirty-first week of pregnancy and not less than 30 days before the expected day of delivery, each woman was taken into the trial and a sealed envelope containing instructions about treatment was opened. As already explained, these instructions, which were decided by a system of random sampling numbers, referred either to the question of premature induction of labour versus spontaneous delivery or to the question of exchange transfusion versus simple transfusion, or both, depending on the particular centre. The instructions were entered on a special record card which also contained space for many other details of the case.

Infants born more than 35 days before the expected day of delivery were entirely excluded from the trials, whether delivery occurred spontaneously or as a result of premature induction of labour.

Premature Induction of Labour

When the instructions called for premature induction of labour this was required to be carried out by artificial rupture of the membranes not more than 35 days, or less than 21 days, before the expected day of delivery. Caesarean section was carried out in a few cases either for obstetrical reasons or because the patient failed to go into labour following rupture of the membranes.

Treatment of the Infant

Infants were transfused only if they were Rh positive and had a positive direct antiglobulin test and if their cord haemoglobin concentration was below 15.6g./100ml. (14.9g./100ml. at centre " N "). Rh negative blood stored for less than seven days was used for all transfusions. The blood used was either a concentrated suspension of group O red cells or whole citrated blood of the same ABO group as the infant.

When exchange transfusion was carried out, a minimum of 50 ml. of blood per lb. body weight was injected. The blood injected was a concentrated suspension of red cells with a haemoglobin concentration of approximately 16g./100 ml. The amount of blood removed from the infant was similar to, but not necessarily identical with, that injected. Exchange transfusion was always carried out within 9½ hours of birth, using the umbilical vein method (Diamond, 1947).

Simple transfusions also were given within 9½ hours of birth, using either the umbilical vein or some other vein; the blood was administered at a slow drip rate. When the cord haemoglobin concentration lay beween 12.6 and 15.5g./100ml. the amount transfused was between 10 and 20 ml. per lb. body weight; when the cord haemoglobin concentration was 12.5g./100ml. or less, the amount was 15 to 25 ml. per lb. body weight.

After the first day transfusions were given, at the discretion of the clinician, solely with the object of relieving anaemia.

At centre " N " a different plan was followed for those infants for whom the instructions called for simple transfusion and whose cord haemoglobin concentration exceeded 11g./100 ml.; in these cases transfusion was not given unless the infant's haemoglobin concentration subsequently fell below 11g./100ml. That is to

say, at centre " N " infants due for simple transfusion received it only if they were anaemic at the time of birth or if they subsequently became anaemic.

Cord Blood Samples

The cord was clamped as soon after birth as possible. A sample was then obtained from the umbilical vein using a dry syringe and needle. The blood was then mixed either with dry heparin or with Wintrobe's oxalate mixture.

Haemoglobin Estimation

Haemoglobin was measured as a 1/200 dilution of oxyhaemoglobin in the M.R.C. photometer (King *et al.*, 1948). 0.5 ml. of blood was taken into an Ostwald pipette and washed into dilute ammonia (0.04 per cent in distilled water) in a 100 ml. volumetric flask. The flask was then filled to volume. The solution was read in the M.R.C. photometer and the haemoglobin value was taken as the mean of six observations.

In order to discover whether comparable haemoglobin determinations were being made at different centres, samples of blood were distributed to the various centres on four different occasions during the 2-year period of the trials. On each occasion a sample of the same blood was sent to the National Physical Laboratory for haemoglobin determination and its result was taken as the correct value for the sample. Each centre took part in these tests on at least two occasions and tested at least four blood samples. In all, 55 results based on the examination of 7 different blood samples were available. All the 7 samples were found by the National Physical Laboratory to have haemoglobin values within the range 91–107 per cent (Haldane). The results can therefore conveniently all be considered together as percentage deviations from true values of approximately 100 per cent. The mean value of all the readings was 1.4 per cent higher than the National Physical Laboratory value. Thirty-two of the 55 values were within ± 5.5 per cent of the National Physical Laboratory value. The standard deviation of the series was 3.8 per cent.

In view of the fact that almost one-half of all the infants in the trial came from centre " N ", attention must be drawn to the fact that at this centre all the readings of the test samples were too high with a mean error of + 5.5 per cent. In the results which follow, all haemoglobin estimations in infants have been given as they were returned by the different centres, without correction.

Later Observations on Infants

On the record card observers were asked to record any untoward signs occurring during the first week of life and to report whether the infants appeared to be normal or abnormal at the age of one month. As many infants as possible were re-examined at the age of 6 months or more, and again at the age of 1 year or more.

Results

Premature Induction of Labour versus Spontaneous Delivery

The analysis in this section is restricted to results from centres at which premature induction and spontaneous delivery were compared according to the system of randomization previously described (i.e., no comparison has been attempted between centres which practised premature induction of labour exclusively and those in which delivery was always allowed to occur spontaneously).

In these centres 118 cases were selected for premature induction and 112 for spontaneous delivery. Unfortunately the analysis of these 230 cases presents some difficulty since the rules prescribed for premature induction were followed strictly in only 77 out of the 118 cases (65 per cent), whereas those for spontaneous delivery were followed in 108 out of the 112 (96 per cent).

Cases have been regarded as not complying with the prescribed rules in either of the following circumstances:

1. If the case was one in which the instructions called for premature induction of labour but the infant was born later than 18 days before the expected day of delivery. There were 41 of these cases.

2. If the case was due for spontaneous delivery but labour was induced more than 10 days before the expected day of delivery. There were 4 of these cases. (This implies that for the

few cases due for spontaneous delivery, where labour was induced less than 11 days before the expected day of delivery, the contravention of rules has been ignored.)

If a mother was due for premature induction of labour and went into premature labour spontaneously, giving birth to an infant 18 to 35 days before the expected day of delivery, the case has been regarded as complying with the rules. (It was considered that for such cases premature induction of labour might well have been carried out within the time limits had the woman not gone into labour spontaneously before induction could be arranged.)

An analysis of the cases for which the rules of the trial were complied with may be invalidated by the much heavier " lapse rate " in the induction group than in the spontaneous delivery group. In particular, it is likely that the 41 cases omitted from the induction group (which were all mature births) represent better than average risks and therefore that an analysis of the remaining cases will be subject to a bias against premature induction. On the other hand, an analysis of all the 230 cases, according to intended treatment, will be likely to underestimate any possible difference in death-rate between the two treatments, since the group intended for induction will include a considerable proportion of cases in which induction was carried out after the prescribed time limit. (For such an analysis see Appendix I.)

An analysis of the 185 cases complying with the rules has previously been published (Mollison and Walker, 1952) and is reproduced here as Table I. In Appendix I reasons are given for believing that this analysis is not seriously invalidated by the high lapse rate in the induction group.

The difference between the two death rates, 12.3 per cent, has a standard error of 6.8 per cent, and is therefore not quite significant at the customary 0.05 level ($P=0.07$)* The 95 per cent confidence interval for the difference extends from – 1.0 per cent to 25.6 per cent; therefore, we may conclude that induction is unlikely to improve the survival rate by more than 1 per cent.

Neonatal deaths and stillbirths have been deliberately added together in this analysis. They should not be considered separately, as premature induction would be expected to raise the proportion of neonatal deaths to stillbirths (as illustrated in Table I).

Rh negative infants. In comparing the relative risks of premature induction of labour and spontaneous delivery, the effects on Rh negative infants must also be considered. In the present series of cases due for premature induction of labour in which the rules were complied with there were, in addition to the Rh positive infants already considered, 17 Rh negative infants, 2 of whom died. However, 1 of these infants died of asphyxia following a retroplacental haemorrhage causing spontaneous delivery at the thirty-fifth week of pregnancy and the death of this infant was therefore not due to premature induction of labour. The other infant died of pulmonary haemorrhage; as its birth weight was 4 pounds 1 ounce its death can be considered to have been due to premature induction of labour.

In the corresponding series due for spontaneous delivery and complying with the rules there were 35 Rh negative infants of whom 1 was

* All the significance tests for differences in proportions which are used in this paper are based on the ratio of a difference to its standard error, regarded as a normal deviate. No continuity correction has been applied.

TABLE I

Comparison of the effects of premature induction and spontaneous delivery for cases complying with rules
(From Mollison and Walker, 1952)

Treatment	No. of cases	Living at one month	Deaths			Death rate per cent
			Neonatal deaths	Stillbirths	Total	
Induced	77	49	22	6	28	36.4
Spontaneous	108	82	12	14	26	24.1

stillborn (cause unknown) and 1 died on the tenth day of life from congenital heart disease.

Exchange versus Simple Transfusion

The analyses in this section are restricted to results from centres at which exchange and simple transfusions were compared according to the prescribed system of randomization. Infants at centre " N ", whose cord haemoglobin concentration was between 11.1 and 14.8g./100ml. inclusive, received either exchange or " late simple " transfusion, as explained earlier. These cases were fully discussed by Mollison and Walker (1952) and are not considered in this section of the present paper.

Infants whose cord haemoglobin concentration exceeded 15.5g./100ml. received no transfusion. Apart from these infants, 71 cases were selected for exchange and 66 for simple transfusion; as in the comparison of premature induction and spontaneous delivery, the analysis is complicated by the fact that the prescribed rules for treatment were followed strictly in only 62 out of the 71 cases due for exchange transfusion (87 per cent) and 57 out of the 66 due for simple transfusion (86 per cent).

Cases have been regarded as not complying with the rules in any of the following circumstances:

1. Failure to measure the haemoglobin concentration of cord blood.
2. Death of the infant before treatment could be given.
3. Giving the wrong type of transfusion, i.e., simple transfusion when the instructions called for exchange.
4. Failure to give the transfusion within 9½ hours of birth, or the use of blood stored for more than 7 days, or of Rh positive blood.
5. The exchange of less than 50 ml. of blood per lb. body weight, if the infant was due for exchange transfusion.

Of the 18 cases in which the rules were not complied with, the infants intended for exchange transfusion fared worse than those intended for simple transfusion. If there was a tendency for those infants with a poor prognosis to be omitted from the exchange group more frequently than from the simple group, a comparison of the cases complying with the rules would be unfair to simple transfusion. On the other hand, an analysis of all the 137 cases, including those not complying with the rules, errs in another direction: any benefit due to exchange transfusion will be under-stated since not all infants due for exchange transfusion actually received this treatment.

Tables II and III show the neonatal death-rate in the cases complying with the rules. (The deaths in fact all occurred within 7 days of birth.)

The difference between the two death rates, 23.9 per cent, has a standard error of 7.9 per cent, and is significant ($P < 0.01$).

Interesting comparisons can be made by subdividing the cases firstly according to the haemoglobin concentration of their cord blood and secondly according to maturity. For this purpose all infants born later than 18 days before the expected day of delivery are considered to be " mature " and all those born between 18 and 35 days before the expected day of delivery are considered to be " immature ". (This term has been used to avoid confusion with " premature ". The term " premature ", except in the phrase " premature induction ", is used throughout this paper to refer to infants weighing 5½ pounds or less at birth.) It may be observed from Table III that the significance of the over-all difference shown by Table II is entirely due to two of the four groups: Immature, haemoglobin concentration greater than 11g./100ml.; and Mature,

TABLE II

Over-all comparison of exchange versus simple transfusion for cases complying with rules
(From Mollison and Walker, 1952)

Treatment	Total	Living at one month	Neonatal deaths	Death-rate per cent
Exchange	62	54	8	12.9
Simple	57	36	21	36.8

TABLE III

Comparison of exchange versus simple transfusion for cases complying with rules, sub-divided according to maturity and haemoglobin concentration.

	Cord haemoglobin concentration g./100 ml.	Exchange transfusion Deaths/Total	per cent	Simple transfusion Deaths/Total	per cent	Difference ± S.E per cent
Immature ...	⩽11	4/10	(40.0)	5/10	(50.0)	10.0 ± 22.3
	>11	0/13	(0)	8/18	(44.4)	44.4 ± 15.9
Mature	⩽11	2/27	(7.4)	6/16	(37.5)	30.1 ± 12.3
	>11	2/12	(16.7)	2/13	(15.4)	−1.3 ± 14.7

N.B. "⩽" = less than, or equal to.

haemoglobin concentration less than, or equal to, 11g./100ml.

A similar analysis by intended treatment, including the 18 cases not complying with the rules, is given in Appendix II. Even this over-cautious analysis suggests an advantage in exchange transfusion.

Causes of death. In Table IV the deaths referred to in Table III are sub-divided into those occurring within 30 hours of birth (" first day ") and those occurring between 2 and 5 days, apparently from kernicterus.

It is immediately apparent that the reduction in mortality following exchange transfusion is due entirely to a reduction in the incidence of kernicterus. (The figures in Table IV differ slightly from those given by Mollison and Walker, 1952; it was stated previously that only 4 out of 8 deaths following exchange transfusion were due to kernicterus but it is now considered more likely that 6 of the 8 deaths were due to this cause.)

Relationship between Cord Haemoglobin Concentration and Chance of Survival

Mollison and Cutbush (1951) observed that, when cases were divided into groups according to their cord haemoglobin concentration, the survival rate bore a sigmoid relationship to the haemoglobin concentration. Since it appears reasonable to expect a zero survival rate when Hb = 0 (and therefore log Hb = $-\infty$), and a survival rate of 100 per cent when Hb = ∞ (and log Hb = ∞), a linear relationship between the probit of the survival rate and the logarithm of the haemoglobin concentration was assumed. The resulting curve is symmetrical when haemoglobin is plotted on a logarithmic scale, but asymmetrical if a linear scale of haemoglobin is used. The same basic assumption is made in the present work. The method of probit analysis is explained in detail by Finney (1952).

The present data have been used to examine the relationship between cord haemoglobin con-

TABLE IV

Deaths in the first week of life following exchange and simple transfusion

	Cord haemoglobin concentration g./ 100 ml.	Exchange transfusion Total	Deaths First day	Deaths 2–5 days (kernicterus)	Simple transfusion Total	Deaths First day	Deaths 2–5 days (kernicterus)
Immature	⩽11	10	0	4	10	0	5
	>11	13	0	0	18	0	8
Mature	⩽11	27	2	0	16	3	3
	>11	12	0	2	13	0	2
		62	2	6	57	3	18

centration and the chance of survival, with and without exchange transfusion.

(a) *Infants not treated by exchange transfusion.* In the first group all infants who either received no treatment, or only a simple transfusion, have been considered together. Thus at one end of the scale it includes moribund infants who were too ill to be treated, and at the other, very mild cases, too mildly affected to need treatment. In between are infants who received either an early simple transfusion (within 9½ hours of birth), or a later simple transfusion, or no transfusion at all.

Infants who were due for an exchange transfusion—according to the rules of the trials—but did not receive one owing to technical difficulties, are not included in this series. However, all infants whose cord haemoglobin concentration exceeded 15.5g./100ml. are included, whether they were in the exchange transfusion or the simple transfusion series, since none of them received transfusion during the first few days of life. Similarly all infants from centre "N" whose cord haemoglobin concentration exceeded 14.8g./100ml. are included.

In this analysis only neonatal deaths have been considered; however 5 cases have been excluded in which it seemed reasonably certain that the infant's death was not related to haemolytic disease. These 5 infants had cord haemoglobin concentrations between 16.1 and 19.5g./100ml.; 2 were considered to have died from asphyxia, 2 from atelectasis and 1 from cerebral haemorrhage.

In Table V the infants not treated by exchange transfusion are subdivided by haemoglobin, maturity and sex, and the survival rate is shown for each sub-group, both as the proportion of survivors to the total and as a percentage. The grouping intervals for haemoglobin are chosen to be equal (to 0.1) on a logarithmic scale.

Details of the curves fitted to the data of Table V are given in Appendix III. These curves are shown in Fig. 1, in which haemoglobin is plotted on a linear scale. The curve for immature males is markedly different from the other three curves and this difference in position is shown in Appendix III to be significant. It appears, therefore, that for infants with haemolytic disease and with a given cord haemoglobin, the hazard is particularly severe in immature males. (The increased susceptibility of males to kernicterus has previously been noted by Diamond, Vaughan and Allen, 1950.)

(b) *Infants treated by exchange transfusion.* The second group includes all infants treated by exchange transfusion. The infants considered here are: (i) all those intended for exchange transfusion and for whom the instructions were correctly followed, and (ii) all those intended for exchange transfusion but who died before the treatment could be given. One infant who was

TABLE V

Proportions of survivals in infants not treated by exchange transfusion

Cases are sub-divided by haemoglobin, maturity and sex; survival rate is shown as a proportion (Surv./Total) and as a percentage of the total.

log. Hb	Cord haemoglobin concentration g./100 ml.	Immature				Mature			
		Males		Females		Males		Females	
		Surv./Total	*Per cent*	Surv./Total	*Per cent*	Surv./Total	*Per cent*	Surv./Total	*Per cent*
0.5–	3.2– 3.9	0/1	*0*	—	—	—	—	0/1	*0*
0.6–	4.0– 5.0	0/1	*0*	—	—	0/1	*0*	—	—
0.7–	5.1– 6.3	—	—	—	—	0/1	*0*	0/1	*0*
0.8–	6.4– 7.9	0/1	*0*	0/1	*0*	1/3	*33*	2/4	*50*
0.9–	8.0– 9.9	2/5	*40*	2/3	*67*	5/6	*83*	2/3	*67*
1.0–	10.0–12.5	1/6	*17*	4/4	*100*	13/15	*87*	9/9	*100*
1.1–	12.6–15.8	17/25	*68*	10/13	*77*	35/39	*90*	28/32	*88*
1.2–	15.9–19.9	14/16	*88*	14/14	*100*	46/49	*94*	55/56	*98*
1.3–	20.0–	—	—	1/1	*100*	1/1	*100*	1/1	*100*
		34/55	*62*	31/36	*86*	101/115	*88*	97/107	*91*

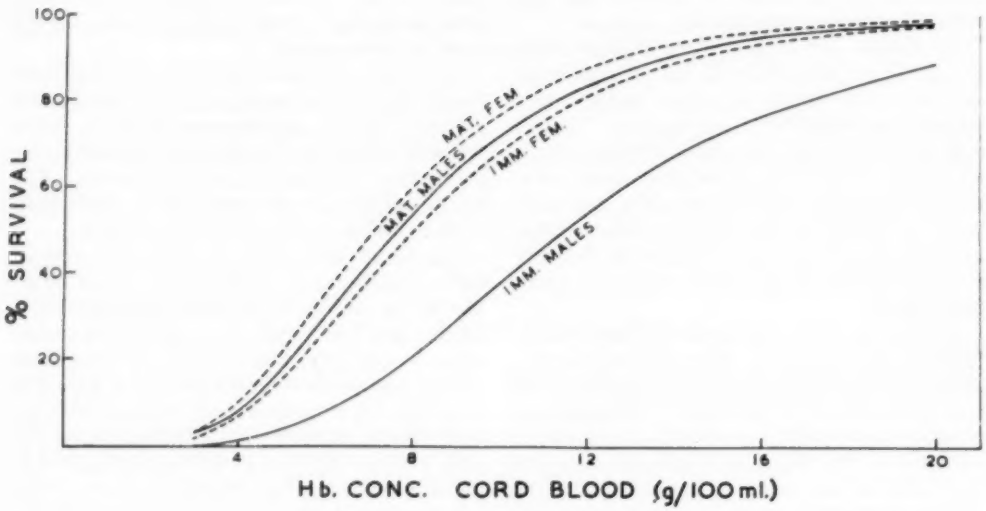

FIG. 1

Curves relating cord haemoglobin concentration to the chance of survival in male and female infants receiving either simple transfusion or no transfusion. "Mat." = mature, i.e., born within 10 days of term; "Imm." = immature, i.e., born 35—18 days before term. Details of the curve-fitting are given in Appendix III.

due for simple transfusion but received exchange has been omitted as have all infants who were due for exchange transfusion but for whom the instructions for that treatment were not correctly followed. This analysis is intended to give the best available description of the results of following a routine of exchange transfusion, allowing for a small proportion of moribund infants who cannot be treated. The analysis refers to neonatal deaths; there were in this series no deaths unrelated to haemolytic disease. The main restriction of the present data is that no information is available for the result of exchange transfusion in cases with a haemoglobin concentration greater than 15.5 g./100 ml. since all such infants in this investigation were untreated.

It should be emphasized that this analysis and that of the preceeding section do not replace the comparison made earlier between simple and exchange transfusion. Such a comparison can strictly only be made in those centres which allocated the two treatments at random. The data for the curve-fitting are not restricted to these centres.

In Table VI the infants treated by exchange transfusion are sub-divided by haemoglobin, maturity and sex, and the survival rate is shown for each sub-group, both as the proportion of survivors to the total and as a percentage. The grouping intervals for haemoglobin are the same as in Table V.

Details of the curves fitted to the data of Table VI are given in Appendix III. Separate curves have been fitted for immature and mature infants, but the results from both sexes have been pooled, as no sex differences were apparent. The fitted curves are shown in Fig. 2. For comparison, Fig. 2 also shows the curves for infants not treated by exchange transfusion, with both sexes pooled.

The estimated survival rates given by these four curves, for different levels of haemoglobin, are shown in Table VII.

TABLE VI

Proportions of survivals in infants treated by exchange transfusion

Cases are sub-divided by haemoglobin, maturity and sex; survival rate is shown as a proportion (Surv./Total) and as a percentage of the total.

log. Hb	Cord haemoglobin concentration g./100 ml.	Immature				Mature			
		Males		Females		Males		Females	
		Surv./Total	*Per cent*	Surv./Total	*Per cent*	Surv./Total	*Per cent*	Surv./Total	*Per cent*
0.5–	3.2– 3.9	—	—	—	—	—	—	0/1	*0*
0.6–	4.0– 5.0	—	—	—	—	—	—	—	—
0.7–	5.1– 6.3	0/1	*0*	1/3	*33*	—	—	—	—
0.8–	6.4– 7.9	1/2	*50*	—	—	3/3	*100*	4/6	*67*
0.9–	8.0– 9.9	1/4	*25*	2/2	*100*	6/6	*100*	5/5	*100*
1.0–	10.0–12.5	4/4	*100*	4/4	*100*	13/14	*93*	11/13	*85*
1.1–	12.6–15.5	6/6	*100*	4/4	*100*	8/8	*100*	8/8	*100*
		12/17	*71*	11/13	*85*	30/31	*97*	28/33	*85*

TABLE VII

Estimated percentage survival rates for various cord haemoglobin concentrations

Cord haemoglobin concentration g./100 ml.	Without exchange transfusion				With exchange transfusion	
		Immature		Mature	Immature	Mature
	Males	Females	Total			
3	0	2	1	2		
4	1	6	4	9		
5	3	15	9	19	7	53
6	8	26	17	32	21	66
7	14	38	26	44	40	76
8	21	49	35	56	60	83
9	29	59	44	66	75	88
10	37	68	53	74	86	92
12	53	80	67	85	96	96
14	66	88	77	91	99	98
16	76	93	84	95	100	99
18	83	96	89	97		
20	88	98	93	98		

For the group of immature infants not treated by exchange transfusion the two sexes are shown separately as well as together, because of the sex difference previously established in this group. Since extrapolation beyond the concentrations of haemoglobin observed in the present data would be dangerous, neither Fig. 2 nor Table VII has been extended beyond these limits.

Detailed comparison from Fig. 2 between groups treated and untreated by exchange transfusion is inadvisable, not only because data are included from centres which did not randomize the treatments, but also because the curves are subject to considerable sampling fluctuations (as may be observed from the width of the confidence intervals for 50 per cent survival levels of haemoglobin, given in Appendix III). Still less do the curves give an adequate indication of the effect of premature induction, for stillbirths which, as we have seen, occur more frequently in spontaneous delivery than in premature induction, are omitted from the data used in Fig. 2. Nevertheless, the curves tend to confirm the observation made earlier, that the advantage of exchange transfusion is particularly noticeable for immature infants with a fairly high haemoglobin concentration and for mature infants with low haemoglobin.

Later Observations on Infants

Of 374 Rh positive infants surviving at the end of the first week of life (see Mollison and Walker,

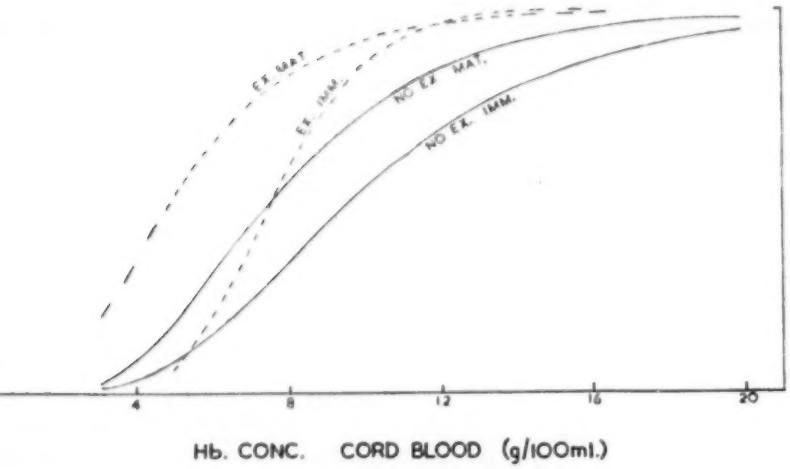

FIG. 2

relating cord haemoglobin concentration to the chance of survival, with varying treat-
"Ex." = exchange transfusion; "No Ex." = simple transfusion or no transfusion;
= mature, i.e., born at term or within 10 days of term; "Imm." = immature, i.e., born
5–18 days before term. Details of the curve-fitting are given in Appendix III.

within the first 6 months of life, 4
ts of kernicterus and 4 from other
e remaining 366 infants, 357 were
the age of 6 months or more. In
progress of infants, clinicians were
ver two questions only: does the
pment appear to be normal for its
ere evidence of motor damage?

infants examined at the age of 6
were 16 whose development was
be subnormal. Of the remaining
om causes unrelated to haemolytic
en the sixth and twelfth month of
f the remainder were re-examined
ges of 1 and 3 years. Four were
bnormal.

f a total of 374 infants surviving
the first week of life, at least 24
r showed signs of damage to the
n. Some details relating to these
given in Table VIII. It may be
ongst the 17 infants considered to
cerebral damage during the first week of life only 10 appeared to be abnormal at the age of 1 month. However 15 of the 17 were recognizably abnormal at the age of 6 months.

Ten infants not referred to in the Table were suspected of having signs of cerebral damage in the first week of life but subsequently developed normally. Five of these infants were jaundiced for long periods (10–30 days) and 5 for only short periods (3–5days). Among these 10 infants there were several who appeared to be spastic in the first week of life but none who displayed opisthotonos.

It has to be borne in mind that a few infants whose cerebral damage was probably unrelated to haemolytic disease have probably been included in Table VIII. For example infants Du/15 and M/37 were never jaundiced and had only serological evidence of haemolytic disease of the newborn.

Effect of treatment on subsequent course of infants. It has been suggested that, although exchange transfusion may increase the imme-

Centre/No.	Sex	M (w
Du/15	F	
Ox/ 7	M	
H/34	M	
SH/19	M	
Du/26	F	
Ox/M26	M	
M/ 5	F	
Du/43	F	
H/21	F	
Br/25	F	
Ca/B2	F	
Cd/10	M	
QC/18	M	
M/ 1	M	
H/58	F	
Nc/22	M	
H/61	F	
Nc/98	M	
H/42	F	
Nc/82	F	
M/37	M	
SH/8	F	
QC/25	M	
SH/17	M	

TABLE VIII

Details relating to 24 infants who had haemolytic disease of the newborn and were subsequently found to be backward

Sex	Maturity (weeks)	Birth weight lb./oz.	Cord haemoglobin concentration g./100 ml.	Treatment	Duration of jaundice (days)	Appeared normal at one month	Signs Five months–11 months	Signs One–three years
				Infants showing signs of motor damage during first week of life				
F	40	7/ 1	19.2	O	0	Yes	Normal	Backward Motor damage
M	39	6/ 6	17.0	O	11	No	Backward	
M	40	6/13	16.7	O	13	No	Backward	
M	36	6/10	16.3	O	10	Yes	Backward	
F	38	7/12	16.0	O	>18	No	Backward: Deaf	
M	39	5/14	15.2	O*	43	No	Backward: Motor damage	
F	40	8/ 0	15.1	S*	26	No	Backward	
F	38	6/11	14.8	S*	33	Yes	Backward	
F	37	4/12	14.4	E*	49	No	Backward: Blind: Deaf	
F	37	6/ 0	12.9	E	21	No	Backward: Spastic	
F	40	6/12	12.4	S	9	Yes	Normal	Ataxic: normal intelligence
M	37	5/13	12.0	S*	11	No	Backward	
M	37	6/ 0	12.0	E	25	Yes	Backward: Spastic	
M	40	7/ 5	10.9	S*	32	Yes	Backward: Holds head back	
F	36	5/ 4	10.3	S	13	No	Backward: Squint	
M	40	6/ 2	9.5	E	> 7	Yes	Backward: Motor damage	
F	37	7/ 0	8.8	E	>16	No	Backward: ?Blind :Squint	
				Infants showing lethargy during first week of life				
M	39	7/ 0	9.8	S	> 7	Yes	Backward	
F	40	6/ 0	7.4	S	>45	Yes	Backward	
F	41	—	6.7	E	120	No		
				Infants appearing normal during first week of life				
M	40	7/15	17.9	O	0	Yes	Normal	Backward at 16 months
F	36	6/ 4	16.7	O	13	Yes	Backward: Hypotonic	
M	36	7/ 9	15.7	O	25	Yes	Normal	Backward
M	36	6/ 3	15.1	E	5	Yes		

* Excluded from the strict comparison of exchange and simple transfusion as set out in Tables II, III, IV, and IX.

diate survival rate in haemolytic disease of the newborn, its use may be associated with an increased incidence of cerebral damage among survivors. The question may be examined by considering the groups presented in Table II above. These infants must be regarded as more severely affected than the average since all had cord haemoglobin concentrations below 15.6 g./100 ml. and thus are particularly suitable for this type of comparison.

In Table IX further information about these infants is presented.

TABLE IX

Incidence of kernicterus in infants selected at random for exchange and simple transfusion

		Total	Deaths on first day of life	Deaths from kernicterus: First week	Deaths from kernicterus: One week to six months	Surviving at six months but backward	Incidence of kernicterus: K/Total	Incidence of kernicterus: Per cent
Exchange transfusion	Immature	23	0	4	1	3	8/23	35
	Mature	39	2	2	1	1	4/37	11
		62	2	6	2	4	12/60	20
Simple transfusion	Immature	28	0	13	0	1	14/28	50
	Mature	29	3	5	0	3	8/26	31
		57	3	18	0	4	22/54	41

It will be seen that, amongst 54 infants treated by exchange transfusion and surviving for more than one week, 2 died of the late effects of kernicterus during the first 6 months of life and 4 others were recognized to have cerebral damage when examined at the age of 6 months. Among 36 infants treated by simple transfusion and surviving for more than one week, 4 were recognized to have cerebral damage. There is, therefore, no evidence that the incidence of cerebral damage among survivors is any greater when exchange transfusion is used than when simple transfusion is used.

In Table IX figures are also given for the over-all incidence of kernicterus; that is to say, of fatal and non-fatal cases. The incidence of kernicterus is twice as high among the infants treated by simple transfusion as among those treated by exchange transfusion. Moreover the incidence of kernicterus in the mature infants treated by exchange transfusion is only about one third of that in the immature infants treated by exchange transfusion.

Incidence of cerebral damage in untreated infants. The incidence of fatal kernicterus in the first week of life in untreated infants—that is to say, infants whose cord haemoglobin concentration exceeded 15.5 g./100 ml. (or 14.8 g./100 ml. at centre "N")—has already been described (Mollison and Walker, 1952). Most of the survivors were followed for at least 6 months. Table X gives an analysis of the over-all incidence of kernicterus; that is to say, not only of the deaths from kernicterus in the first week of life, already reported, but of 1 further death from kernicterus during the first 6 months and of 8 infants found to be backward during the first 6 months or later. Six of these 8 infants had been deeply jaundiced and were suspected of having kernicterus from the first week of life onwards. However 2 infants, both mature and having cord haemoglobin concentrations above 17.6 g./100 ml. (Du/15 and M/37, see Table VIII), were never jaundiced and were not considered to be abnormal until after they had reached the age of 1 year. It seems probable that they were not suffering from the effects of kernicterus.

It will be noted that the over-all incidence of kernicterus was about twice as high among the immature infants (16 per cent) as among the mature infants (7 per cent). It will also be observed that there were no definite cases of

TABLE X

Incidence of kernicterus in infants whose cord haemoglobin concentration exceeded 15.5 g./100 ml. (14.8 g./100 ml. at centre "N"). None of these infants was transfused during the first few days of life.

	Cord haemoglobin concentration g./100 ml.	Dying in first 6 months			Surviving at six months but backward	K/Total	Per cent
		Total	Kernicterus	Other cause	Not followed			
Immature	14.9–17.5	38	4	2	2	3	7/34	21
	17.6–21.5	12	0	1	2	0	0/9	0
		50	4	3	4	3	7/43	16
Mature	14.9–17.5	101	6	4	5	3	9/92	10
	17.6–21.5	40	0	2	1	(0)*	0/37	0
		141	6	6	6	3	9/129	7

* There were 2 infants in this group who were backward, but probably from causes unrelated to kernicterus (see text).

kernicterus among 46 infants whose cord haemoglobin concentration exceeded 17.5 g./100 ml.

Relation between cord haemoglobin concentration and the incidence of kernicterus

It has been suggested that "the incidence of kernicterus is virtually independent of the degree of anemia" (Diamond *et al.*, 1950). However, the present data suggest that the incidence of kernicterus is greater in infants with low cord haemoglobin concentrations. The over-all incidence of kernicterus in the 222 mature infants not treated by exchange transfusion (see Table V) was assessed by including as cases of kernicterus not only those dying from this cause but also those surviving with signs of cerebral damage, as judged by examination at six months. Infants dying on the first day of life and those dying from causes unrelated to haemolytic disease, as well as those not followed for as long as six months, were excluded. The overall incidence of kernicterus was as follows:

Cord haemoglobin concentration g./100 ml.	Incidence of kernicterus K/Total	Per cent
3.2– 9.9	6/13	46
10.0–15.8	13/92	14
more than 15.9	5/98	5

DISCUSSION

Premature Induction versus Spontaneous Delivery

The present results suggest that it is unlikely that premature induction of labour increases the chance of the survival of an infant with haemolytic disease of the newborn and that, on the contrary, such a practice may diminish the survival rate. It must be pointed out that in these trials no attempt was made to select cases in which premature induction of labour might have been specially indicated; and the results certainly do not show that premature induction never increases the infant's chance of survival. Nevertheless, since the severity of the disease varies strikingly in successive infants born to the same mother and since the severity of the disease cannot be reliably predicted before birth, it is difficult to see how cases could be specially selected for premature induction even if it could be shown to be beneficial in severe cases. Unless some new controlled trials produce clear evidence of the value of premature induction of labour in selected cases there is little doubt that the safest course is to abandon this method of treatment for haemolytic disease of the newborn. This decision is reinforced by considering that, as a result of inducing labour prematurely, an occasional Rh negative infant may die from a cause related to prematurity.

A further consideration is the effect on the mother. Artificial rupture of the membranes more than 3 weeks before term may fail to induce labour promptly and further interference may be required. In the present series, out of 77 cases in which premature induction was called for, Caesarean section was resorted to in 10 instances because labour did not begin after artificial rupture of the membranes.

Exchange versus Simple Transfusion

The practical implications of the results have already been discussed (Mollison and Walker, 1952). However, some interesting points emerge from the new analysis presented here.

Further evidence is produced to support the previous observation that in haemolytic disease of the newborn the chance of survival is closely related to the haemoglobin concentration of the cord blood (Mollison and Cutbush, 1951). In the present paper the effects of maturity and of exchange transfusion upon this relationship are displayed graphically (Fig. 2). A study of this figure helps to explain previously held differences of opinion. For example, Diamond and his co-workers became convinced of the value of exchange transfusion at a time when others thought its advantage doubtful. The paper by Allen, Diamond and Vaughan (1950) records that premature induction of labour was abandoned as a method of treatment at about the same time as exchange transfusions were begun; for example, in 1946 labour was induced before the thirty-eighth week in 50 per cent of the patients and exchange transfusion carried out in only 10 per cent of the infants. In 1948 labour was induced before the thirty-eighth week in only 18 per cent of the mothers but exchange transfusions were given to 69 per cent of the infants. Fig. 2 shows that for any given haemoglobin level the greatest improvement in survival is produced by changing from simple transfusion in immature infants ("No Ex. Imm.") to exchange transfusion in mature infants ("Ex. Mat.").

Conversely, in Britain, the practices of premature induction of labour and of exchange transfusion were introduced simultaneously and many felt that this combination of treatment was no better than that of complete conservatism. Reference to Fig. 2 shows that this attitude was largely justified since the curves for exchange transfusion in immature infants and for no exchange in mature infants are similar, the combination of exchange transfusion and immaturity appearing to be a little better at high haemoglobin levels, but inferior at low haemoglobin levels.

Indications for exchange transfusion. The policy of withholding treatment from all infants whose cord haemoglobin concentration exceeds about 15 g./100 ml. is seen to be far from satisfactory. Without treatment, the incidence of kernicterus in such infants is about 7 per cent if they are mature and about 16 per cent if they are immature. It seems probable that most of these infants would develop normally if treated by exchange transfusion.

If premature induction of labour is avoided, the number of infants born prematurely will be small and it is feasible to treat all such infants by exchange transfusion, irrespective of their cord haemoglobin concentration. On the other hand the number of mature infants with cord haemoglobin concentrations exceeding 15 g./100 ml. is large: in fact, about 40 per cent of the total number of cases of haemolytic disease of the newborn. Since more than 90 per cent of these infants will develop normally if left untreated, the use of exchange transfusion for all of them is wasteful of time and submits many infants to an unnecessary risk. The present data suggest that a cord haemoglobin concentration exceeding 17.5 g./100 ml. is a strong indication that the infant will not develop kernicterus if untreated. Other factors to be considered in deciding which cases to transfuse and which to leave have been discussed elsewhere (Mollison and Cutbush, 1954).

SUMMARY

The results of controlled trials of treatment of haemolytic disease of the newborn carried on in Great Britain and Ireland between 1949 and 1951 are further analyzed and the follow-up of the infants during their first year of life is described. Previous conclusions about the superiority of exchange transfusion over simple

transfusion are reinforced; not only were there more survivors among infants treated by exchange transfusion but the incidence of cerebral damage among the survivors was low and was confined mainly to infants born prematurely. It is also concluded that routine premature induction of labour probably increases mortality.

We should like to thank all those who conducted these trials for empowering us to publish this report; we should also like to acknowledge our debt to Miss Marie Cutbush, who gave us most extensive help in collecting the data and in drawing up the tables on which the analyses were based.

APPENDIX I

The Effect of the High Lapse Rate in the Premature Induction Group on the Comparison with Spontaneous Delivery.

In the analysis shown in Table AI all cases have been included which were due either for premature induction of labour or for spontaneous delivery, whether or not the treatment was carried out strictly according to the rules. (As in the earlier analysis, only results from those centres at which the two treatments were compared by randomization are considered.)

The difference between the two death rates, 5.5 per cent, has a standard error of 5.9 per cent and is not significant ($0.3<P<0.4$). The 95 per cent confidence interval for the difference extends from −6.1 per cent to 17.1 per cent; at this level of significance it may be concluded that a policy of induction, applied to only about two thirds of the cases, is unlikely to improve the survival rate by more than 6.0 per cent.

It has already been stated that this analysis is likely to under-estimate any possible difference in death rate between the two treatments. The extent to which the analysis of cases complying with the rules (presented earlier in Table I) is likely to be biased by the high lapse rate among the cases intended for premature induction is next considered. The effect cannot be estimated at all certainly without some knowledge of the reasons for the failure to carry out induction within the prescribed time limits. In the following argument the fairly plausible assumption is made that the reason for this failure in any particular case is unrelated to the severity of the disease. The cases which would have been left until too late for induction can then be regarded as an effectively random sample of all the 118 cases intended for induction.

Even so, the death rate in the premature induction group in Table I will be subject to an upward bias; for, as stated above Table I, cases intended for induction, in which delivery occurred spontaneously 18 to 35 days before the expected day of delivery, have *not* been excluded from that table. A certain number of infants must thus have been unwittingly included who were intended for induction but for whom no arrangements for premature delivery would, in fact, have been made and who were therefore included only because they were born prematurely. This group of infants, being less mature, would tend to have a less favourable prognosis than those excluded.

On the assumption stated above, the bias due to the high lapse rate could be corrected if the number of infants included in this way in Table AI and the number of deaths among them could be estimated and subtracted from the totals in Table AI.

Consider the following sub-division of the spontaneous births in cases complying with the rules, by date of delivery. Here (1+5)/14 means 1 neonatal death and 5 stillbirths out of 14 cases.

35–18 days before E.D.D.	Later than 18 days before E.D.D.	Total
(1+5)/14	(11+9)/94	(12+14)/108

The cases which were omitted from the induction group may be written:

Later than 18 days before E.D.D.
(5+3)/41

The rough proportionality of the deaths in these 2 groups born later than 18 days before the expected day of delivery accords with the belief that the lapsed cases can be regarded as a random sample of the cases intended for induction and therefore of the whole group of cases in the trial. Since the spontaneous cases also are a random sample of all cases in the trial, the numbers of cases and deaths corresponding to these 41 in the 35 to 18 day period can now be estimated; thus:

$$(1+5)/14 \times \frac{41}{94} = (0.4+2.2)/5.7$$

TABLE AI

Comparison of cases intended for premature induction and those intended for spontaneous delivery.

Treatment	No. of cases	Living at one month	Neonatal deaths	Stillbirths	Total	Death rate Per cent
Induced	118	82	27	9	36	30.5
Spontaneous	112	84	13	15	28	25.0

The original figures for induction, complying with the rules, were (22+6)/77 (Table I). These are now corrected by subtracting (0.4+2.2)/5.7, giving (21.6+3.8)/71.3; i.e., 25.4 deaths out of 71.3 cases, a death rate of 35.6 per cent. The estimated correction is therefore small (*cf.* the uncorrected death rate of 36.4 per cent) and it seems likely that the analysis of Table AI is not far wrong.

APPENDIX II

Comparison of Cases Intended for Exchange Transfusion and those Intended for Simple Transfusion

As stated earlier, the analyses of Tables II and III may be unfair to simple transfusion. Tables AII and AIII present similar analyses of all the 137 cases intended for either exchange or simple transfusion, including those for which the rules were not strictly followed. This analysis is likely to err in the other direction in that any benefit due to exchange transfusion will tend to be understated. As before, the analyses are restricted to results from centres at which exchange and simple transfusions were compared on randomly selected groups. Infants whose cord haemoglobin concentration exceeded 15.5 g./100 ml. are excluded since they received no transfusion.

TABLE AII

Over-all comparison of cases intended for exchange and those intended for simple transfusion

Intended treatment	Total	Living at one month	Neonatal deaths	Death-rate per cent
Due for exchange	71	59	12	16.9
Due for simple	66	45	21	31.8

The difference between the two death rates, 14.9 per cent, has a standard error of 7.3 per cent and is significant ($0.02<P<0.05$). Even this over-cautious approach, therefore, demonstrates an advantage in exchange transfusion.

In Table AIII the results are sub-divided by cord haemoglobin concentration and maturity. Again the exchange: simple contrast is evident in only two of the four groups—the same two as in Table III.

APPENDIX III

Probit Analyses for Survival Rate Curves

Probit lines relating Y, the probit of the survival rate, to x, the logarithm to base 10 of the cord haemoglobin concentration (expressed in g/100ml.), have been fitted to the data shown in Tables V and VI. Since the haemoglobin concentrations are grouped in these Tables, the grouping corrections given by Tocher (1949) were applied but their effect is so small as to be negligible.

(a) *Infants not treated by exchange transfusion* (Table V and Fig. 1). Parallel lines were fitted for the four groups shown in Table V. Their equations are as follows:

Immature	Males:	$Y = -0.318 + 4.993x$
	Females:	$Y = 0.468 + 4.993x$
Mature	Males:	$Y = 0.565 + 4.993x$
	Females:	$Y = 0.718 + 4.993x$

The test for non-parallelism shows small and non-significant differences between slopes ($\chi^2=0.83$ on 3 d.f.; $0.8<P<0.9$); there seems, therefore, no objection to the fitting of parallel lines to the four groups. The common slope, 4.993, has a standard error of 0.807, and is thus highly significant.

The position of each curve may be characterized by the haemoglobin concentration corresponding to a survival rate of 50 per cent. The estimates of these 50 per cent survival levels, with their 95 per cent confidence limits, are shown below (the odds are 19 to 1 that the stated limits include the true value).

		Estimated haemoglobin concentration for 50 per cent survival (g/100ml.)	95 per cent confidence limits
Immature	Males	11.6	9.5—13.7
	Females	8.1	5.6—10.6
Mature	Males	7.7	5.8— 9.3
	Females	7.2	5.1— 8.9

There is very little difference between the 50 per cent survival points for immature females, mature males and mature females but that for immature males is significantly higher than any of the other three.

(b) *Infants treated by exchange transfusion* (Table VI and Fig. 2). As a preliminary analysis, parallel lines were fitted to the four groups as in (a). The test for non-parallelism again showed non-significant differences between the four slopes, but it was observed that the slopes for the two immature groups were steeper than those for the mature groups. The difference between the two pairs was again not significant $\chi^2=2.70$ on 1 d.f.; $0.1<P<0.2$); but as this difference had been observed in an earlier analysis (of the data used in the exchange: simple comparison), where it actually reached significance, it seemed safer in the present instance to fit independent lines for the immature and mature groups. As no sex differences were apparent, and as the immature group was rather small, both sexes were pooled for this analysis. The equations of the resulting lines are as follows:

Immature:	$Y = -2.530 + 8.619x$
Mature:	$Y = 2.033 + 4.354x$

TABLE AIII

Comparison of cases intended for exchange and those intended for simple transfusion sub-divided by maturity and haemoglobin concentration

	Cord haemoglobin concentration g/100ml	Exchange Transfusion Deaths/Total	Simple Transfusion Deaths/Total	Diff. ± S.E. per cent
Immature	≤11	5/12 (41.7)	5/10 (50.0)	8.3 ± 21.3
	>11	2/17 (11.8)	8/21 (38.1)	26.3 ± 14.4
Mature	≤11	2/27 (7.4)	6/17 (35.3)	27.9 ± 11.9
	>11	3/15 (20.0)	2/18 (11.1)	−8.9 ± 12.5

N.B. "≤" = less than, or equal to. Percentages are shown in parentheses.

The slope for the immature group, 8.619, has a standard error of 2.756; that for the mature group, 4.354, has a standard error of 1.886 and is therefore only just significant ($0.02<P<0.05$).

The estimates of the haemoglobin concentrations corresponding to 50 per cent survival, with their 95 per cent confidence limits, are as follows:

	Estimated haemoglobin concentration for 50 per cent survival (g/100ml.)	95 per cent confidence limits
Immature	7.5	5.1—8.9
Mature	4.8	0.1—6.9

The two curves plotted in Fig. 2 for the exchange transfusion groups and the estimated survival rates shown in Table VII for these groups are obtained directly from the probit lines given above. The corresponding curves and rates for the groups not treated by exchange transfusion have been derived from the probit lines given in (a) above, by taking percentage survival rates mid-way between those obtained for the two sexes separately. The resulting curves do not correspond exactly to any probit lines, but close approximations are provided by the probit lines mid-way between those given for the two sections separately in (a). The equations of these approximate probit lines are:

Immature: $Y = 0.075 + 4.993x$
Mature: $Y = 0.642 + 4.993x$

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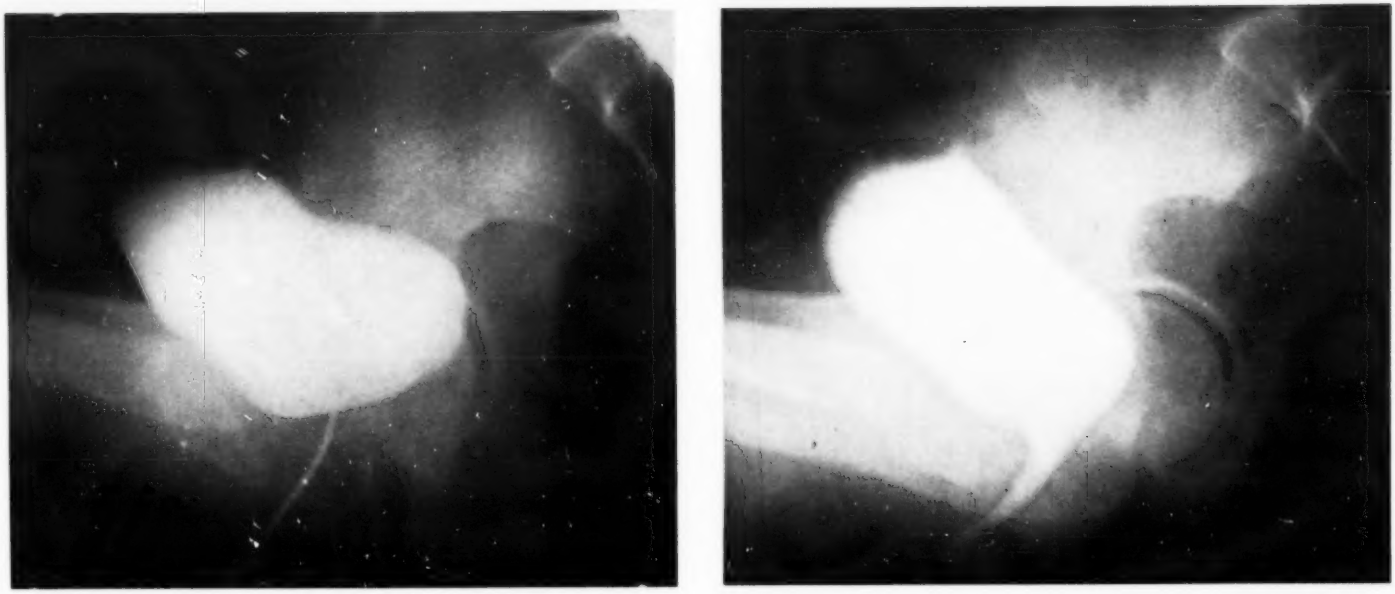

(*a*) (*b*)

FIG. 1

Lateral cysto-urethrograph in a nulliparous woman with normal bladder function.

(*a*) Resting easily.

(*b*) Micturition well established. Catheter removed from urethra which is outlined by the radio-opaque fluid being voided. The ovoid bladder outline and crenation of its posterior margin are indicative of detrusor muscle contraction.

H.R.

OBSERVATIONS ON MICTURITION IN THE FEMALE*

BY

HENRY ROBERTS, M.D., M.R.C.O.G.

From the Department of Obstetrics and Gynaecology, University of Liverpool

INTRODUCTION

DURING a study of the anatomical changes associated with stress incontinence and its cure, the function of micturition in women has come under observation. Two hundred and twenty women, continent and incontinent, parous and nulliparous, were investigated by cystoscopy, cystometry and cystourethrography, and the urinary apparatus in cadavers of all ages was examined by naked eye dissection and serial section microscopy. The results and inferences are here assembled and correlated with other observations gleaned from the literature to present a composite picture of the mechanism of micturition, and of its disturbances, in Woman.

THE PHYSIOLOGY OF MICTURITION

Accommodation of the Bladder to Filling

Cystometric studies show that, as the bladder gradually fills with urine discharged from the ureters, its muscle wall maintains its tone at a constant low level so that the intravesical pressure remains below 10 cm. of water (Fig. 2). Desire to micturate is usually experienced when the volume of fluid within the bladder is between 200 and 300 ml. In children and untrained animals a detrusor contraction sets in at this point and the bladder empties automatically. In adults and trained animals both the action of the detrusor muscle and the desire to void are inhibited if evacuation is inconvenient. Filling then proceeds, but still without much change in the intravesical pressure until the limit of bladder distension is approached when there is a sharp rise in intravesical pressure. The desire to micturate then recurs more insistently, and ultimately becomes so urgent that the subject finds it difficult to continue inhibiting the detrusor muscle.

When the detrusor contracts and micturition begins the pressure rises to 30–50 cm. of water, this pressure being maintained until the emptying process is practically complete. Voluntary bearing-down effort can raise the pressure still further up to a total of 60–100 cm. of water. Indeed there is nearly always an initial peak rise due to the contraction of the abdominal muscles which is the first event in micturition.

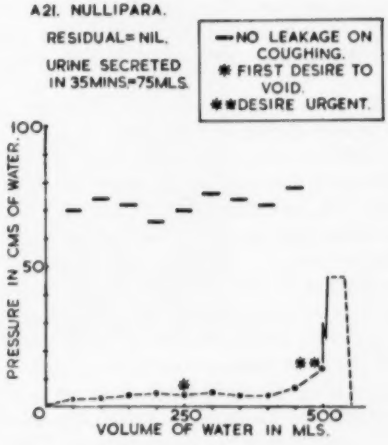

FIG. 2
Normal cystometrograph

If the intra-abdominal pressure is suddenly raised by coughing, or other violent muscular activity, the intravesical pressure is temporarily raised from the resting pressure of less than 10 cm. water to 70 cm., and sometimes even to 100 cm., of water. Normally, however, continence is maintained despite the pressure being as high as, if not higher than, it is during

* William Blair-Bell Memorial Lecture delivered to the Royal College of Obstetricians and Gynaecologists, May 15, 1953.

micturition. The onset of micturition therefore does not come about because an increasing intravesical pressure forces the sphincter mechanism; it must result from the active release of this mechanism.

The Cause of the Urge to Micturate

Distributed throughout the bladder walls, but concentrated mainly in the region of the trigone and internal urethral meatus, are stretch receptor nerve endings. These receptors, which were first demonstrated by von Zeissl (1893, 1901), respond to the rate of filling as well as to the volume of fluid in the bladder, but *not* to an increase in intravesical pressure as was previously thought. If the bladder fills quickly desire may be experienced at a lower volume.

Frequency of desire, and even constant desire to urinate, which occur in cases of local lesions of the bladder wall and urethra such as cystitis, urethritis, Hunner's ulcer, polypi, calculi, and tuberculosis are explained by the fact that such lesions stimulate the stretch receptor nerve endings, either directly or by irritating the muscle coat of the bladder and making it hypertonic.

Radiological Changes in the Bladder and Urethra during Micturition

(*a*) *Before micturition* (Figs. 1 and 3). When the patient is standing or sitting quietly with the bladder full, its base (including a small area in front of the internal urethral meatus) lies almost parallel to, and 1–2 cm. above, a line joining the lower margin of the symphysis pubis to the tip of the fifth sacral segment. The urethra joins it to form well defined anterior and posterior angles, the latter measuring approximately 100°. During strong physical effort there is a slight descent of the bladder base but the urethro-vesical relationship remains normal. There is never any escape of urine into the urethra, and continence is maintained at the urethro-vesical junction.

(*b*) *At the onset of micturition* (Fig. 4). Radiological studies at the beginning of micturition show that the bladder assumes an ovoid shape and that its posterior outline becomes crenated. Both these changes are the result of detrusor contraction, the latter representing indentations caused by the contracting fasciculi of muscle. These features persist throughout the whole time that urine is being voided.

The internal urethral meatus rotates downwards and backwards to bring the trigone and upper urethra into line and at the same time it assumes a funnel shape. This funnelling is the result of loss of the posterior urethrovesical angle, the anterior one being preserved.

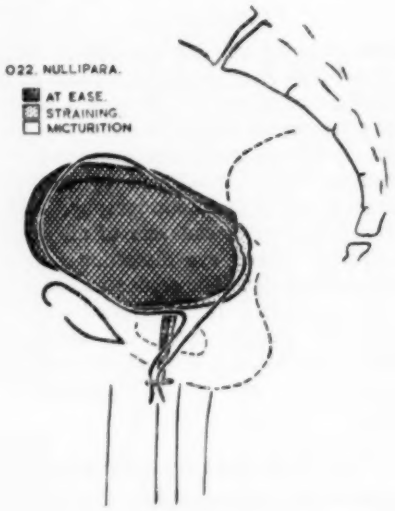

FIG. 3

Superimposed tracings of radiographs in a woman with normal bladder function. Insignificant changes on straining but downward movement of the bladder base, obliteration of the posterior urethro-vesical angle and dilatation of the urethra during micturition.

(*c*) *Micturition established*. When micturition is well established the posterior urethro-vesical angle disappears completely, and the whole of the upper urethra and the bladder base are in line between two fixed points which are situated at the supravaginal cervix and at the triangular ligament (Fig. 5). The urinary stream which, in the upper urethra, is practically parallel to the plane of the pelvic brim, is thus directed downwards in its lower course (Figs. 1, 3 and 6).

Later in micturition the posterior urethro-vesical angle becomes partially restored (Fig. 7) but the dilatation of the urethra, although diminished, remains.

FIG. 4

Cysto-urethrograph taken early in micturition. Obliteration of the posterior urethro-vesical angle and funnelling of the internal urethral meatus already present. Ovoid outline with crenation of the posterior margin indicates that the detrusor muscle is contracting.

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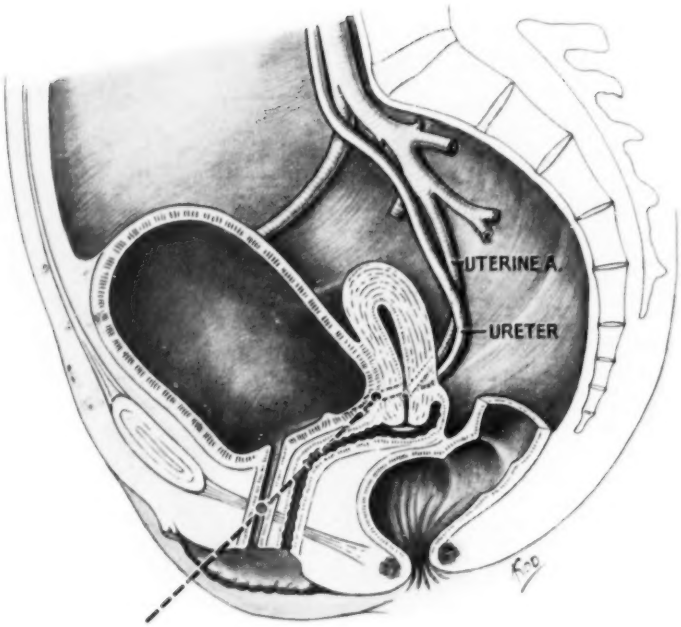


FIG. 5

Diagrammatic representation of the relations of the pelvic organs based on radiographic studies. The two dots indicate the upper and lower fixed points at the supravaginal cervix and triangular ligament respectively. The line joining these points indicates the line of the posterior wall of the urethra and the trigone of the bladder during micturition.

FIG. 6

Cysto-urethrograph showing micturition well established. Detrusor contraction present and the posterior urethro-vesical angle is obliterated. The urethra is dilated and the urinary stream angulated downwards at the level of the triangular ligament. (By courtesy of *Amer. J. Obstet. Gynec.*)

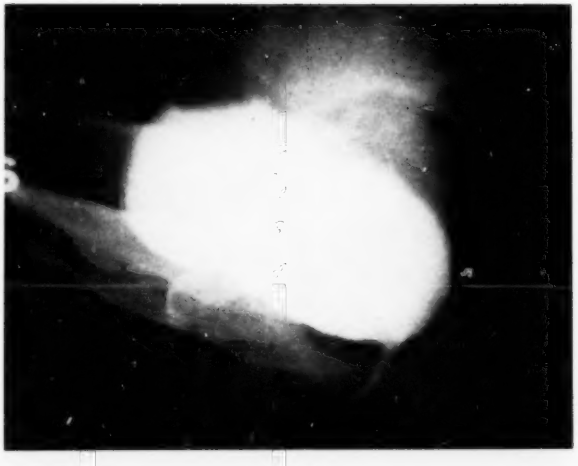
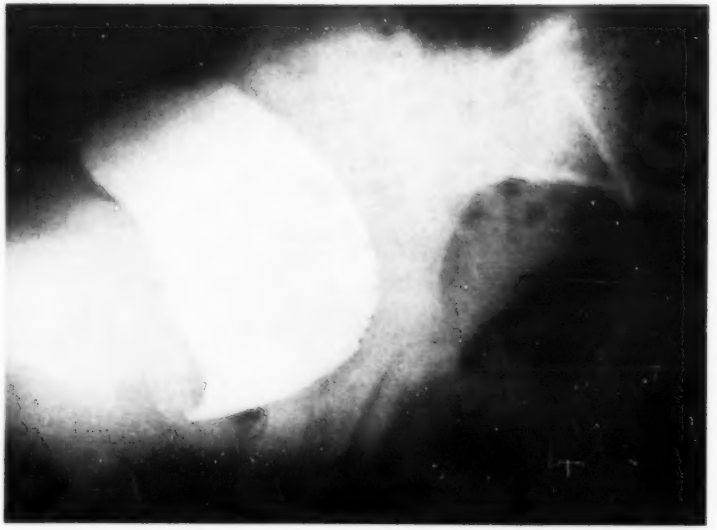


FIG. 7

Cysto-urethrograph later during micturition. Partial restoration of the posterior urethro-vesical angle with decrease in dilatation of the urethra.

(*a*)



(*b*)

(*c*)

FIG. 8

Cysto-urethrographs before and during an unsuccessful attempt to pass urine.

(*a*) Straining down. Bladder base and urethra are normal.

(*b*) Unsuccessful attempt to micturate. Exaggeration of the normal funnelling of the upper urethra, the opaque fluid being held at the level of the triangular ligament. Crenation of the posterior margin of the bladder indicates that the detrusor is contracting.

(*c*) Superimposed tracings of (*a*) and (*b*).

If, because of modesty or other reasons, a woman fails to pass urine despite a genuine effort to do so, it is because the compressor urethrae is not relaxed. In such case the detrusor contracts and the urethra dilates as low as the triangular ligament but no farther. The compressor urethrae can therefore successfully withstand the force exerted by the detrusor (Fig. 8). In the same way, if a woman is asked to stop voiding before the bladder is empty, interruption of the stream takes place at the level of the compressor urethrae, detrusor contraction and dilation of the upper urethra persisting for an appreciable time after the arrest (Fig. 9).

The Sphincter Mechanism

Bladder control depends upon the sum of the resistance offered by each of the muscular components which make up what has been called the " urethal resistance " (Griffiths, 1891, 1895).

The *involuntary* muscle layers of the bladder wall are continued downwards into the urethra with their relative positions reversed (Fig. 11); thus the circular layer comes to lie outside the longitudinal. The inner longitudinal muscle of the urethra may also receive some fibres from the muscle of the trigone. No anatomical sphincter exists at the internal meatus but a complicated interlacing arrangement* of the involuntary fibres at this level prevents the outflow of urine.

There is general agreement regarding the structure and position of the compressor urethrae component of the *intrinsic voluntary* muscle of the urethra. Voluntary muscle fibres are also found above the triangular ligament (Fig. 10). These were noted by Henlé (1856) and even earlier by Guthrie (1834). Immediately above the triangular ligament they embrace the front of the urethra and pass backwards to the lateral vaginal walls. Higher up, the fibres encircle the urethra diagonally, extending backwards and upwards to gain insertion into the bladder base immediately behind the internal urethral meatus (Fig. 12).

The results of this investigation go to show that, contrary to the views generally expressed, the levatores ani have no direct insertion into the urethra (Fig. 13), and any support they offer is indirect by way of their insertions into the anterolateral sulci of the vagina. Contraction of these muscles pulls the anterior vaginal wall and urethra forwards and upwards. Relaxation allows them to rotate backwards and downwards. Nor is the urethra supported by pubocervical fascia; histological sections show that there is no tissue intervening between it and the vaginal musculature (Fig. 15), an observation previously recorded by Blair-Bell (1910) and Goff (1948). Laterally, the urethra, bladder base and vagina, like the uterus, are connected to the pelvic walls by strong condensations of endopelvic connective tissue.

The Interpretation of the Foregoing Observations

An attempt is now made to integrate the anatomical, radiological and cystometric findings in order to trace the sequence of events that occurs in the bladder and urethra during micturition.

Micturition is initiated by a momentary holding of the breath, contraction of the abdominal muscles and diaphragm and, what is more important, by an *active* relaxation of the pelvic muscular diaphragm.† Relaxation of the voluntary muscles of the urethra and of the pelvic floor allows the urethro-vesical junction to move downwards and backwards.

Immediately afterwards, and possibly because this movement of the urethro-vesical junction acts as a trigger, the detrusor muscle of the bladder is released from its inhibition. Contraction of the detrusor results in the bladder becoming ovoid in shape and this raises the intravesical pressure still further.

The muscles of the bladder and urethra are co-ordinated to provide the organ with a

* It has been suggested that the muscles are arranged in the form of anterior and posterior slings (see Fig. 11).

† This bearing down effort is different from the one which occurs during coughing or similar " stress ", for in such a crisis the forceful contraction of the abdominal musculature is accompanied by a protective contraction of the pelvic floor.

property of polarity such as is seen in the uterus. When the bladder contracts the involuntary muscles of the internal meatus and urethra relax, the urethra opening from above downwards. The presence of this automatic polarity is demonstrated by the fact that, even when the compressor urethrae fails to relax and obstructs the outflow of urine, the dilatation of the rest of the urethra still occurs, and is even exaggerated (Fig. 8).

Ordinarily, however, the voluntary as well as involuntary muscles relax and the force exerted by the increased intravesical pressure is directed into the internal meatus which is now in the most dependent part of the bladder.

Angulation of the urethra occurs at the point where the lower urethra is fixed to the subpubic arch by the triangular ligament, and this ensures that the urinary stream is conveniently directed mainly downwards.

The outflow of urine is maintained at a steady pressure until almost the end of micturition by the detrusor contraction alone. It may, however, be accelerated by voluntary contraction of the abdominal muscles. Once the stream of urine is well established partial restoration of the posterior urethro-vesical angle occurs, and the funnelling of the internal meatus and dilatation of the urethra become less manifest. This may mark a gradual return of muscle tone.

When micturition is complete, the tone of the whole urethra returns, the internal sphincter closes and the posterior urethro-vesical angle is restored. The last few drops of urine are expelled from the urethra by the deliberate contraction of the voluntary muscles in and around the urethra.

During micturition the lower ends of the ureters are temporarily obstructed by contraction of the muscle of the bladder wall and of the interureteric bar, but the ureteric flow commences again when the bladder is empty and these muscles relax.

The Posterior Urethro-vesical Angle

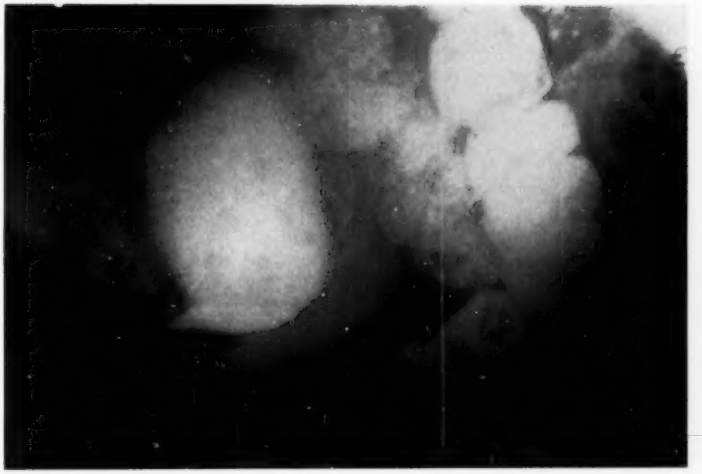
In the foregoing description no attempt is made to explain the mechanism whereby the posterior urethro-vesical angle is obliterated during micturition. Yet this feature is the most important single anatomical change in micturition. Indeed, as emphasized elsewhere (Jeffcoate and Roberts, 1952a, b), maintenance of this angle is essential to continence, and its disappearance under any circumstances other than micturition leads to stress incontinence. An understanding of the muscular control of this angle therefore becomes of great significance.

The posterior urethro-vesical angle might depend on the action of either voluntary muscles or involuntary muscles, or both.

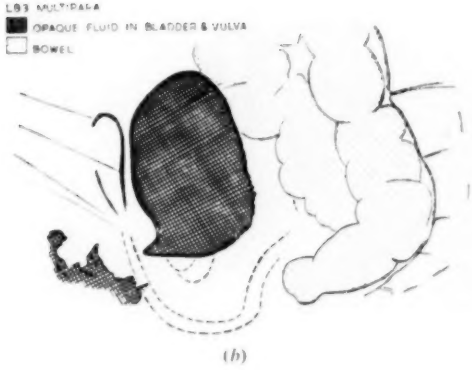
(*a*) *Voluntary muscles.* The insertion of offshoots of the levatores ani into the anterolateral sulci of the vagina might play a part (Fig. 14). The diagram suggests that contraction of these muscles pulls forward the anterior vaginal wall in which the urethra is embedded, thus creating the angle. Relaxation of these muscles allows the angle to disappear. Such relaxation undoubtedly takes place at the onset of micturition when the angle is lost, but it is difficult to believe that these simultaneous occurrences have an important cause and effect relationship because in all degrees of utero-vaginal prolapse without stress incontinence the angle is preserved, and this is true despite the fact that prolapse must be associated with profound weakening or disturbance of the accessory muscles. Observations such as this, as well as the fact that it is difficult, if not imposible, to restore the angle by plastic operation on accessory muscles (Jeffcoate and Roberts, 1952 a, b), strongly suggest that the angle is a function of the intrinsic musculature, either voluntary or involuntary.

The compressor urethrae component of the intrinsic voluntary muscles of the urethra cannot possibly influence the posterior angle, but the voluntary fibres above the triangular ligament, which Kennedy (1946) designated "the muscle of micturition", might well operate. The tangential arrangement of these fibres suggests that when they contract they tend to create the posterior urethro-vesical angle, their relaxation leading to its disappearance. This concept is opposite to the one postulated by Kennedy who suggested that the muscle precipitated rather than prevented the escape of urine from the bladder.

[continued on page 627



(*a*)



(*b*)

FIG. 9

Cysto-urethrograph immediately after interruption of the outflow during micturition.

(*a*) Radiograph showing evidence of detrusor contraction and dilatation of the upper urethra. The barium shadow in the bowel is not significant.

(*b*) Tracing of (*a*).

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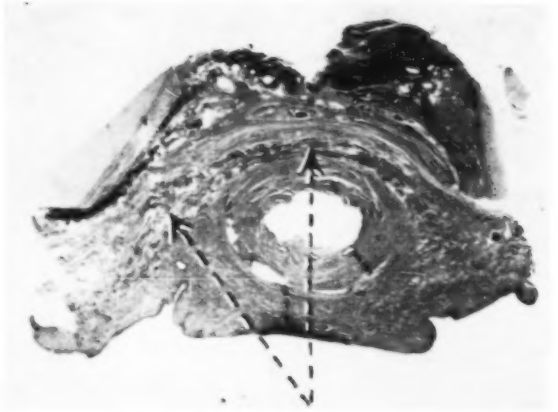

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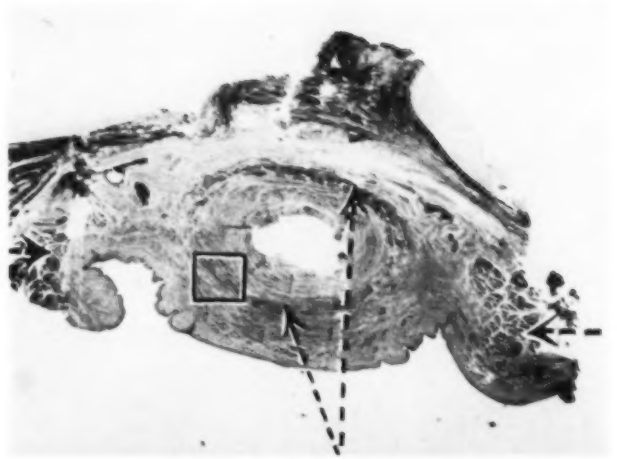


(*b*)

(*c*)

FIG. 10

Photomicrographs of the forepelvis of a 10-months-old female infant showing the distribution of the *intrinsic voluntary muscle* (I.V.M.) in the upper urethra.

(*a*) Immediately above the triangular ligament. The fibres embrace the front of the urethra and pass backwards lateral to the vaginal walls.

(*b*) Midway between the triangular ligament and the internal urethral meatus. Voluntary muscle fibres encircle the urethra in the outer circular involuntary layer. Note the insertion of the levatores ani (L.A.) into the antero-lateral sulci of the vagina.

(*c*) High power view of the striated muscle fibres.

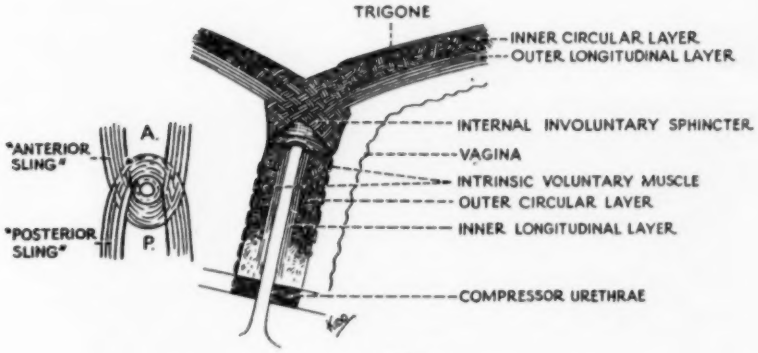


FIG. 11

Diagram showing the arrangement of the *involuntary muscles* of the bladder base and urethra. Inset represents a possible arrangement of the muscular slings.

(By courtesy of *Amer. J. Obstet. Gynec.*)

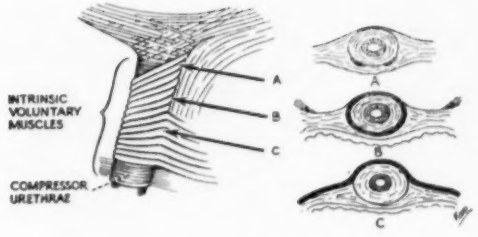


FIG. 12

Diagram showing the arrangement of the *intrinsic voluntary muscles* of the urethra.

(By courtesy of *Amer. J. Obstet. Gynec.*)

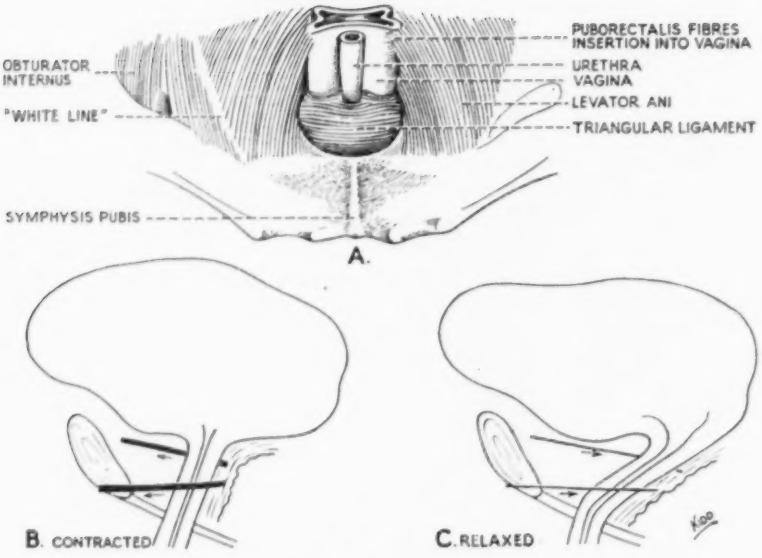


FIG. 13

Diagram showing the relationships of the *levatores ani* to the urethra and vagina (A). Insets B and C show respectively the effect on the urethra and bladder base of contraction and relaxation of these muscles.
(By courtesy of *Amer. J. Obstet. Gynec.*)

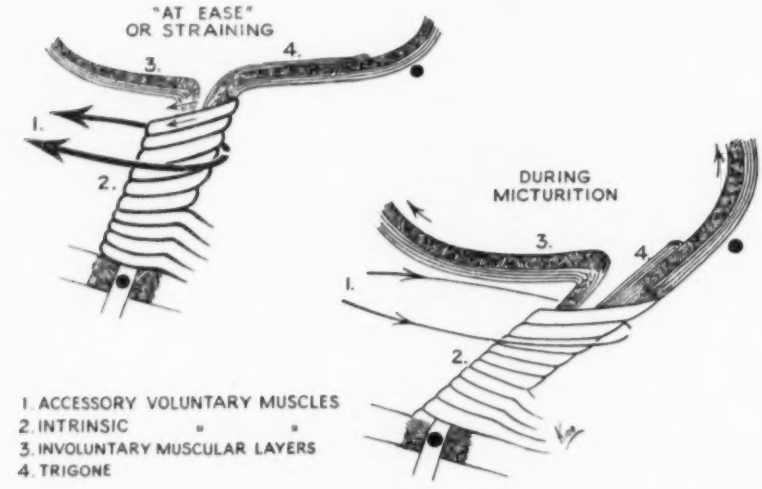


FIG. 14

Diagrammatic representation of the probable effect of the various muscular components upon the posterior urethro-vesical angle.
(By courtesy of *Amer. J. Obstet. Gynec.*)

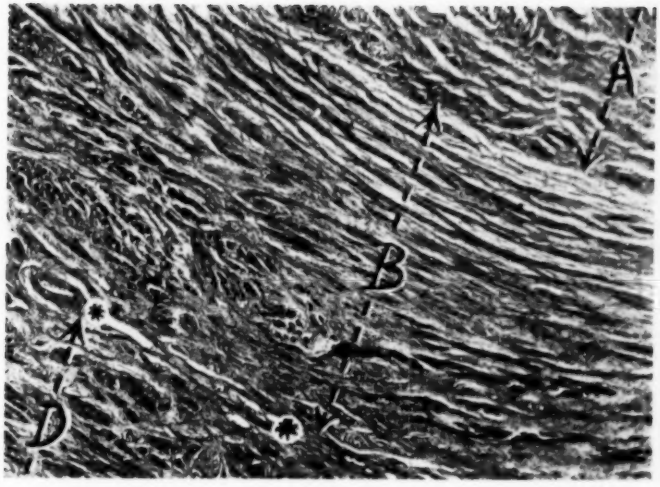


FIG. 15

Photomicrograph of the posterior wall of the urethra and anterior vaginal wall above the level of the triangular ligament to show both the involuntary and voluntary muscle layers (see Fig. 10).

A. Internal longitudinal involuntary layer of the urethra.

B. External circular involuntary layer of the urethra. At the periphery the larger dark staining fibres of the intrinsic voluntary muscle intermingle with the involuntary fibres.

C. Thin vascular layer separating the urethra from the vagina (*).

D. Outer smooth muscle layer of the anterior vaginal wall.

Note the absence of any intervening connective tissue between the urethra and vagina.

H.R.

FIG. 16

Radiograph of a parous woman with a *moderate cystocele without incontinence*, taken with the patient straining down. In spite of descent of the bladder base and upper urethra the posterior urethro-vesical angle remains.

FIG. 17

Cysto-urethrograph of a woman with a *moderate* cystocele showing forward projection of the stream of opaque fluid during micturition because of undue laxity of the triangular ligament.

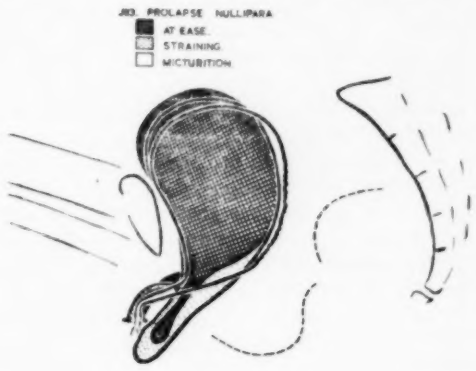


FIG. 18

Superimposed tracings of radiographs in a nulliparous woman with a *severe degree of utero-vaginal prolapse*. Descent of the lower part of the bladder on straining, but the posterior urethro-vesical angle remains normal. Note the effect of the detrusor in alignment of the bladder base and upper urethra during micturition.

(*b*) *Involuntary muscle.* Although there is no proof, it is not unreasonable to suggest that the angle might be maintained merely by good tone of the involuntary muscle around the internal meatus and the urethra itself. Relaxation of these muscles, associated with contraction of the detrusor muscle, coincides with loss of the posterior urethro-vesical angle at the time of micturition.

It was suggested by Wesson (1920) and Young and Wesson (1921) that the trigone in man is continued downwards into the urethra, and that when it contracts it pulls open the posterior lip of the internal meatus. Such an action could also obliterate the posterior angle. However, in woman, the trigonal muscle is extremely thin, it is continued down the urethra only as part of the internal longitudinal layer and it is doubtful whether it has any specific action.

It is not yet possible to draw any firm conclusion as to the musculature responsible for obliteration and restoration of the posterior urethro-vesical angle and it may well be that many components, voluntary and involuntary, normally play a part. Nevertheless, the evidence so far available goes to show that the angle is essentially a function of intrinsic muscles of the internal meatus and urethra rather than of accessory ones.

DISTURBANCES OF MICTURITION IN PROLAPSE

Anatomical Changes

Varying degrees of descent of the bladder base and upper urethra in cases of prolapse are easily demonstrated by lateral cysto-urethrography (Figs. 16, 18, 22, 24, 27). As reported in detail elsewhere (Jeffcoate and Roberts, 1952a, b) loss of the posterior urethro-vesical angle, either at rest or on straining, is a characteristic of stress incontinence. No matter how gross be the dislocation of the upper urethra and bladder from its retropubic position in prolapse *without* stress incontinence, the posterior urethro-vesical angle is preserved and the relationship of the upper urethra to the bladder is normal.

Sometimes there is displacement of the lower urethra because of injury to the triangular ligament. This becomes apparent during micturition when the urinary stream is directed more forwards than usual (Fig. 17). In most

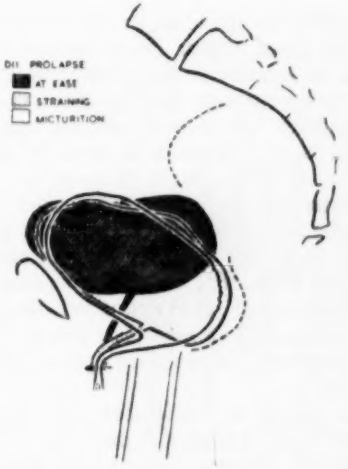


FIG. 19

Superimposed tracings of radiographs in a woman with *utero-vaginal prolapse* without incontinence. Marked descent of the base on straining, but the posterior urethro-vesical angle remains normal. During micturition there is the normal finding of loss of the posterior urethro-vesical angle.

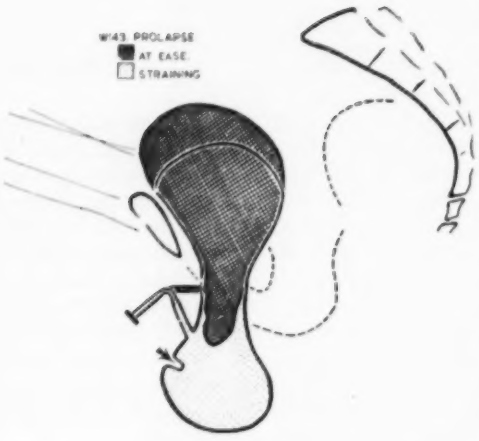


FIG. 20

Superimposed tracings of radiographs in a woman with a *very large cystocele*. Indentation caused by Mercier's bar (arrow) on straining is absent at ease. Constriction at the introitus accounts for the hour-glass bladder outline.

cases, however, the lower urethra remains fixed and the upper urethra rotates around it. The degree of angulation thus created at the level of the triangular ligament depends on the degree of cystocele. In severe prolapse the upper urethra is at a lower level than the external meatus. Nevertheless, in all cases, the process of micturition is essentially normal and is characterized by loss of the posterior urethro-vesical angle and the other changes previously described (Figs. 18, 19, 24). One striking radiographic feature of gross cystocele is that the full bladder assumes an hour-glass shape (Fig. 20). The constriction is produced by the grip of the introitus.

The ureters are displaced and sometimes dilated in severe degrees of prolapse. Indeed as the bladder descends behind and between the lower ends of the ureters there is a considerable drag on the ureters—so much so that they pull on the interureteric bar—raising it to form a ridge that is easily seen on cystoscopy or on cystography (Fig. 24). This bar is often described as being "hypertrophied" in these cases, but this can hardly be a complete description of the pathology because it tends to disappear immediately the cystocele is corrected by temporary replacement or by operation (Fig. 20). This is not to deny that the prominence of the bar is in part explained by hypertrophy (see later).

Hydroureter due to prolapse is characterized by absence of dilatation of the distal pelvic ureter, but the evidence goes to show that this is not because the ureters are constricted by the uterine arteries, as has been suggested. Unless the uterus descends without the bladder, the lower end of the ureter descends with the uterine artery until both lie almost parallel, one crossing the other obliquely (Fig. 25). Ureteric obstruction must therefore be either the result of the pressure of the genital hiatus as suggested by Halban and Tandler (1907) or, even more likely, it is the result of a combination of factors such as back pressure from urethral kinking and hypertrophy of the bladder detrusor muscle; attentuation of the distal ureters by traction; and traction on the cardinal ligaments by the

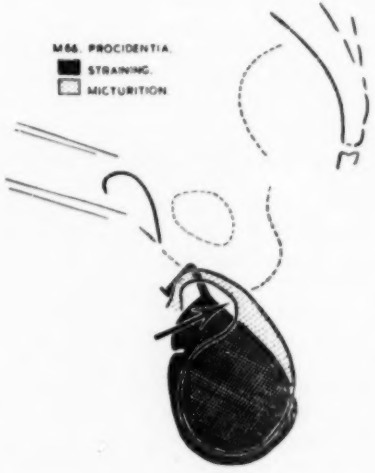
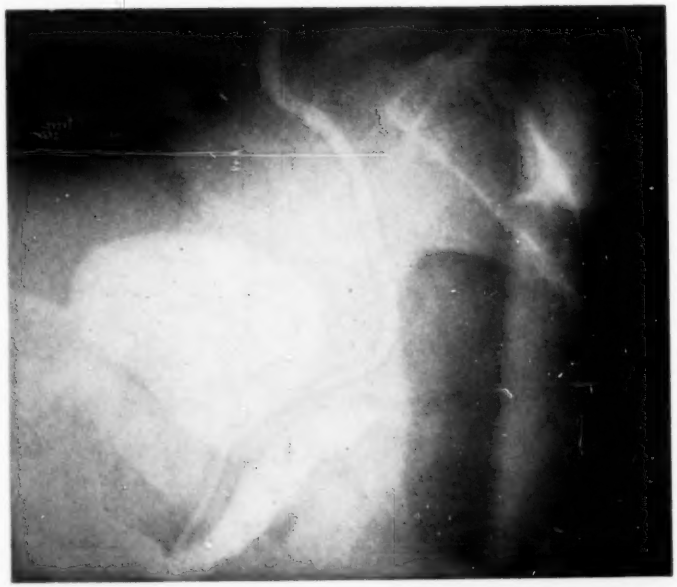
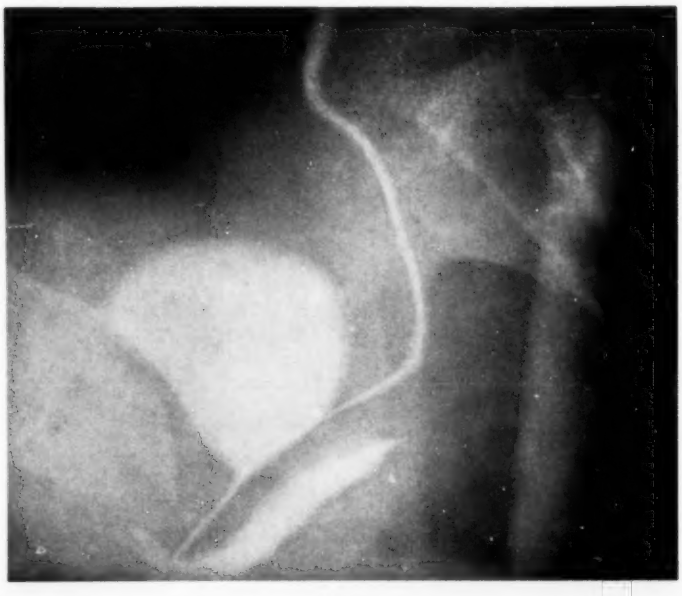


FIG. 21

Superimposed tracings of radiographs of a case of *procidentia*. Angulation of the urethra so marked that digital pressure on the front of the prolapse was necessary to relieve the obstruction during micturition. The indentation and displacement thus caused is indicated by an arrow.



(*a*)



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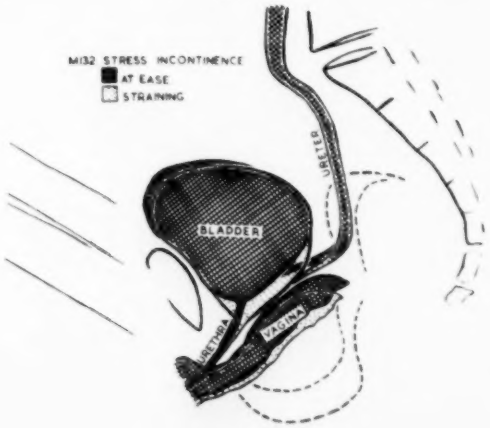


(*c*)

FIG. 22

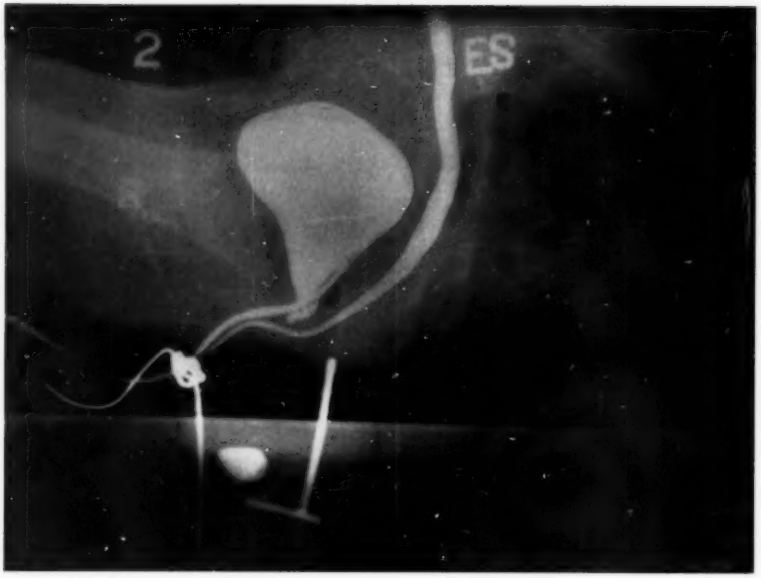
Cysto-urethrograph, colpograph and right ureterograph in a woman with a *slight degree of vaginal prolapse with well-marked stress incontinence.*

(*a*) At ease. Slight funnelling of the urethro-vesical junction.

(*b*) Straining. Exaggeration of the funnelling with descent of the urethro-vesical junction and obliteration of the posterior urethro-vesical angle.

(*c*) Superimposed tracings of (*a*) and (*b*) to show the displacement of the urethra, bladder base, vagina and lower ureter on straining.

H.R.



(*a*)

FIG. 24

Cysto-urethrograph, hysterograph, and right ureterograph in a woman with *procidentia.*

(*a*) *At ease.* The dependent part of the bladder, which is filled with non-opaque residual urine, contains a small quantity of radio-opaque medium. Note absence of kinking of the ureter which is narrow in its distal pelvic course.

(*b*) Tracing of (*a*)

(*c*) *Straining.* Further descent of the bladder and uterus which are almost entirely outside the pelvis. Indentation of the base caused by Mercier's bar. Posterior urethro-vesical angle remains normal.

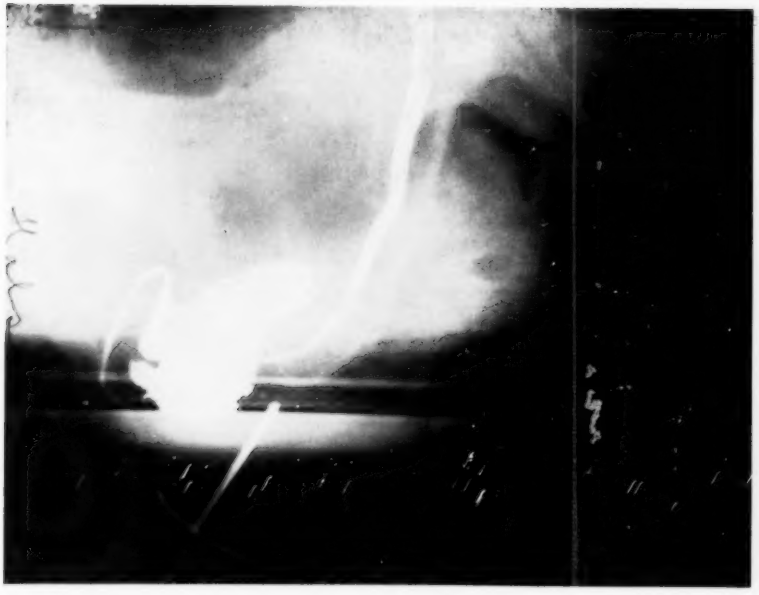
(*d*) Tracing of (*c*).

(*e*) *Micturition.* Both soft rubber and ureteric catheters removed. Marked crenation of the posterior margin of the bladder due to contraction of the hypertrophied detrusor in an effort to overcome the obstruction caused by the kinking of the urethra. The posterior urethro-vesical angle is obliterated and there is loculation of sodium iodide below the persistent indentation of Mercier's bar.

(*f*) Tracing of (*e*) showing fluid levels.

H.R.

(c)



(e)

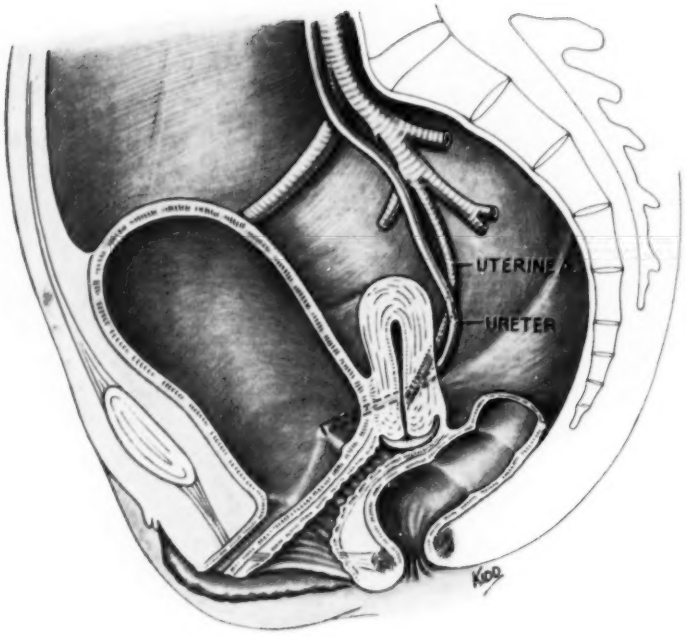


FIG. 23

Diagrammatic reconstruction of the relations of the pelvic organs in mild vaginal prolapse with stress incontinence based on radiological studies. Main area of descent is in front of Mercier's bar. (Compare with Figs. 5 and 25.)

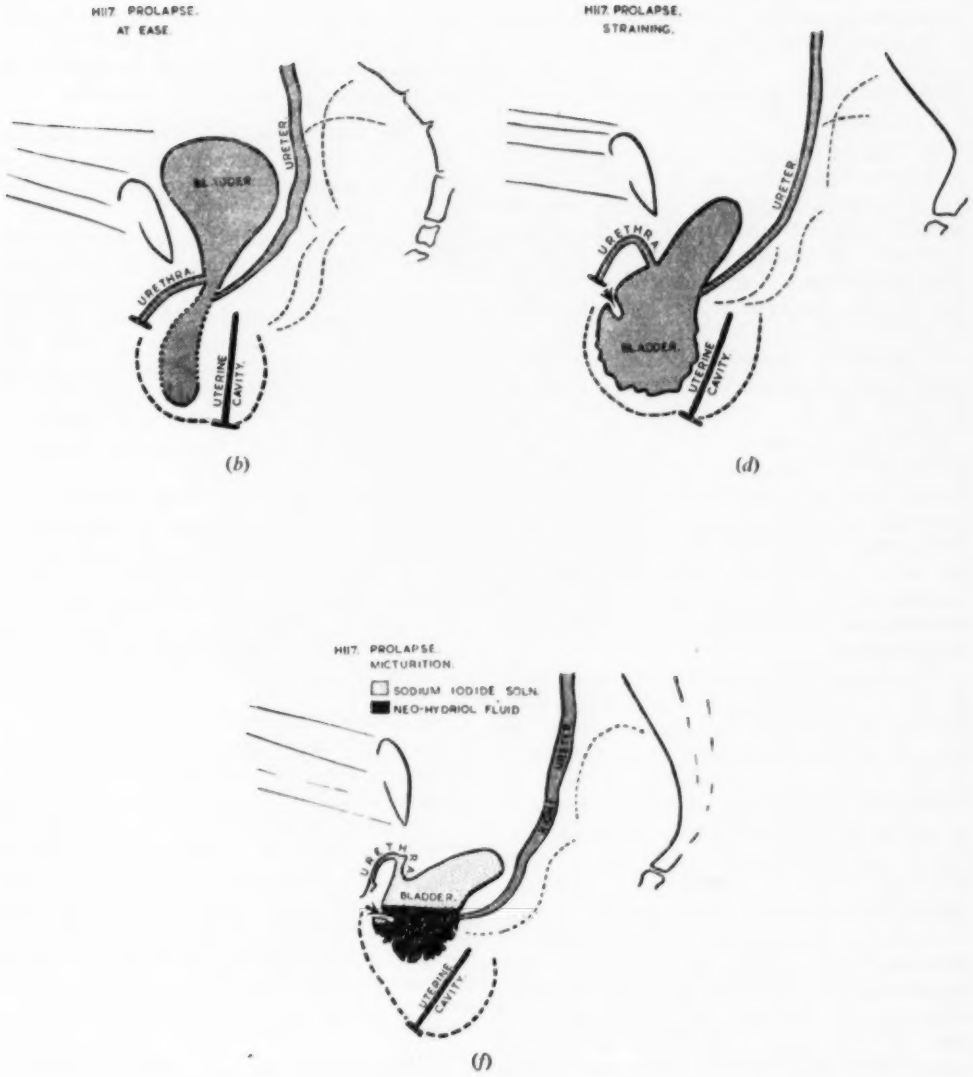


FIG. 24—*continued.*

descending uterus with consequent narrowing of the ureteric canals. Either of the last two possibilities would explain the absence of dilatation of the lower part of the ureter.

Interpretation of disturbances of the urinary apparatus

(1) *Diurnal frequency of micturition* in proprolapse is due to the drag on the bladder base which occurs with the upright posture, and this directly stimulates the stretch receptor nerve endings in the bladder wall. This symptom is more prominent and troublesome if the cystocele involves the more sensitive trigone of the bladder in front of Mercier's bar.

Occasionally, however, diurnal frequency may in part be explained by incomplete emptying of the bladder; a feature of gross cystocele.

(2) *Urgency incontinence.* This term refers to precipitate micturition, that is, the bladder empties itself in part or whole almost immediately the woman experiences desire. She may fail to inhibit the detrusor long enough to enable her to reach a lavatory. This symptom is not peculiar to prolapse and is common when local irritative lesions are present in either the bladder or the urethra.

The condition differs from stress incontinence in that: (*a*) It may occur without physical stress and is accompanied by contraction of the detrusor muscle, (*b*) a strong and urgent desire to pass urine is present immediately before incontinence, (*c*) the volume of fluid which escapes at any one time is much larger, (*d*) leakage only occurs when the bladder is full whereas stress incontinence can be demonstrated when the bladder contains only a small quantity of fluid.

(3) *Stress incontinence.* The anatomical changes present in stress incontinence and their significance are described in detail elsewhere (Jeffcoate and Roberts, 1952a, b). Briefly it may here be stated that stress incontinence occurs when the posterior urethro-vesical angle is temporarily or permanently obliterated—that is when the change characteristic of micturition occurs at rest or under stress (Figs. 22 and 23). This symptom does not depend on the degree and type of genital prolapse—nor on the position of the bladder and urethra in relation to other structures. In a few cases, however, stress incontinence may occur without loss of the posterior urethro-vesical angle, and in these it is either because a cystocele is of a rare type best described as a diverticulum of the trigone, or the urethro-vesical junction is funnelled.

(4) *Incomplete emptying.* A woman suffering from severe cystocele usually finds it difficult to empty the bladder completely for the following reasons:

(*a*) Kinking of the urethra at the triangular ligament causes some degree of obstruction unless the contraction of the detrusor straightens the urethra sufficiently to allow urine to pass (Figs. 18, 24). Some patients get over this difficulty by applying digital pressure on the front of the prolapse during micturition (Fig. 21).

(*b*) Evacuation of the dependent part of the bladder is even more difficult if the bladder is hour-glass in shape (Fig. 20).

(*c*) Hypertrophy, which occurs as part of the hypertrophy of the detrusor in response to urethral obstruction (Fig. 26), and, more especially, the drag on the lower ends of the ureters in severe prolapse, convert Mercier's bar into a ridge which is so prominent as to form a dam across the bladder behind which urine loculates (Fig. 24).

(5) *Urinary tract infection*

Incomplete emptying of the bladder leads to stasis of urine which favours the occurrence of cystitis. This may extend upwards to give rise to pyelitis or pyelonephritis especially as the ureters themselves are displaced and sometimes dilated. Frequency which is both nocturnal and diurnal nearly always means that prolapse has become complicated by urinary tract infection or by some other lesions of the bladder wall such as Hunner's ulcer (Fig. 27).

Conclusion

Urinary symptoms are very common in gynaecological practice, and their elucidation requires the greatest care. Often it is difficult to be certain even of what the complaint is. If the nature of the complaint is clear, its explanation and interpretation in terms of anatomy and pathology can be difficult. Knowledge of the

FIG. 25

Diagrammatic reconstruction of the relative dispositions of the pelvic viscera in procidentia without incontinence based on radiological observations and on the anatomical studies of Halban and Tandler (1907). Note the dam formed across the bladder by the traction of the ureters on the interureteric bar. Main area of descent is behind Mercier's bar.

H.R.

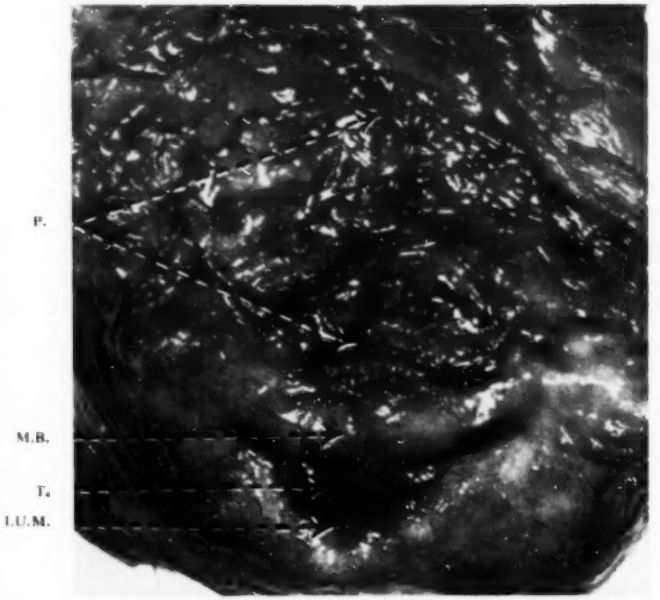


FIG. 26

Photograph of the bladder base removed at autopsy from a woman with a severe degree of utero-vaginal prolapse without incontinence. Note the hypertrophy of the bladder wall and particularly of Mercier's bar (M.B.). Also the absence of any distortion of the internal urethral meatus (I.U.M.) and of the trigone (T.). The main area of prolapse (P.) is entirely behind Mercier's bar.

FIG. 27

Cysto-urethrograph in a woman with a slight cystocele with marked diurnal and nocturnal frequency, urgency incontinence, and dysuria due to Hunner's ulcer. She had been previously operated upon unsuccessfully for "stress incontinence". Apart from slight descent of the bladder base and a small bladder capacity the appearances are normal.

(By courtesy of *J. Obstet. Gynaec. Brit. Emp.*)

mechanism of bladder and urethral function assists in this—as does an awareness of the morbid anatomy present. Indeed without these, treatment by surgical or physiotherapeutic methods is empirical and its results unpredictable and often unsatisfactory. These observations are presented in the hope that their clinical application may be of some value in gynaecological practice. Some of the work reported is confirmatory rather than original, but in the interests of clarity the number of references to other writers is limited. The author, however, wishes to express his indebtedness and appreciation to the many authorities consulted but not mentioned by name.

The work embodied in this lecture was carried out under the invaluable direction and guidance of Professor T. N. A. Jeffcoate. I am also indebted to Drs. P. H. Whitaker and E. L. Rubin and their X-ray departmental staffs, for their continued support and assistance, and to the medical and nursing staffs of the Liverpool Royal Infirmary and Women's Hospital, for their constant help and co-operation. The expenses were defrayed by a generous grant made by the Research Committee of the Board of Governors of the Liverpool United Teaching Hospitals.

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THE VOLUME OF HUMAN AMNIOTIC FLUID

BY

R. G. HARRISON, M.A., D.M.

AND

PERCY MALPAS, Ch.M., F.R.C.S., F.R.C.O.G.

From the Departments of Anatomy and Obstetrics and Gynaecology
University of Liverpool

THERE are on record a number of detailed investigations of the variations in the volume of the amniotic fluid throughout pregnancy in various domestic and laboratory animals such as the pig, sheep and rabbit (Paton, Watson and Kerr, 1907; Jacqué, 1906). The volume of human amniotic fluid at or near term has likewise been determined by various workers (Haidlen, 1887; Lehn, 1916; Dieckmann and Davis, 1933), but apart from a paper by Vonnegut (1928) there are no records of the volume changes throughout pregnancy. There are perhaps two reasons for this lack of information, one the scarcity of suitable material, the other the assumption that the function of the liquor amnii is purely passive, to provide a fluid environment for the foetus, and to play a part in the mechanism of labour.

The immediate objects of the present inquiry were to determine what changes take place in the volume of the liquor amnii in the first 15 weeks of pregnancy, and how far such changes can be correlated with various measurements of the foetus. The inevitable and readily appreciable dearth of material prevented determinations later than the fifteenth week. On the other hand the investigation did cover that phase of pregnancy in which the foetus is at greatest risk, the phase in which spontaneous abortion is most likely to occur. Vonnegut (1928) was able to record 32 comparable determinations extending over the whole course of pregnancy and his results are sufficiently documented to include them with our own observations in a composite graph (Fig. 8). Vonnegut did not analyze his data or express them graphically, and made no attempt to evaluate their significance.

MATERIAL AND METHODS

Material from 12 pregnancies was available for study. The duration of the pregnancies ranged from 8 to 15 weeks. Six of the specimens were obtained by abdominal hysterotomy, the embryos being removed in an intact amniotic sac. Two of the specimens were spontaneous abortions with an intact amnion. Four specimens were obtained by hysterectomy. Most of the pregnancies were terminated on account of phthisis—in view of modern trends a diminishing source of material—while 3 of the hysterectomies were performed on account of a recent prefrontal leucotomy.

In each case the volume of the liquor amnii was estimated by simple puncture of the amnion and drainage into a measuring cylinder. The crown-rump (C.R.) length, weight and volume of each foetus were then measured. The foetal volume was determined by water displacement in the case of the smaller embryos, by the application of Archimedes' principle in the case of the larger. The various data are shown in Table I.

RESULTS

(1) *Volume of Liquor and Crown Rump Length*

The C.R. length of the foetus is perhaps the most reliable measure of the duration of each pregnancy. When the volume of the liquor amnii is plotted against the C.R. length in mm. (Fig. 1), the relationship is curved. The correlation coefficient (r) for this relationship is 0.915, indicating a significant correlation between the two factors.

(2) *Volume of Liquor and Age of Foetus*

If the volume of the liquor is plotted against the age of the foetus, as estimated from the C.R. length, as in Fig. 2, the relationship is also curved, as might be expected. The correlation coefficient, 0.896, again indicates a significant correlation between the volume and the foetal age.

TABLE I

Age of embryo in weeks	C.R. length in mm.	Volume of liquor amnii ml.	Volume of foetus ml.	Weight of foetus in g.
8	28	10.5	3.5	3.5
10	51	18	12	12.4
10	53	62	20	19
11	62	64	36	38.2
11	63	36	25	25.6
12	70	71	31	31.6
13	77	102	44	46.4
13	80	76	60	58.7
13.5	85	84	60	62.6
14	90	150	58	59
14.5	95	180	130	132.4
15	102	148	90	95

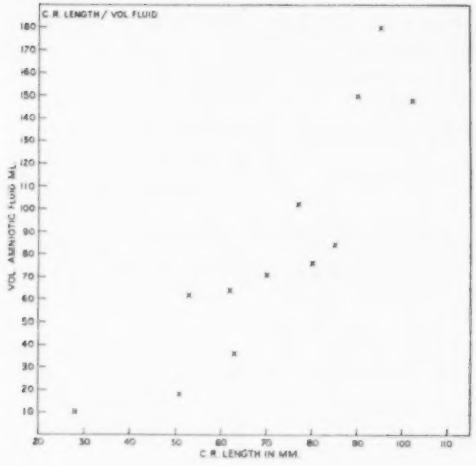

FIG. 1

Graph showing the relationship between volume of liquor amnii and C.R. length of the foetus in the first 15 weeks of pregnancy. The graph is quite clearly curved.

(3) *Volume of Liquor and Volume of Foetus*

The relation between the volume of the liquor amnii and the foetal volume is linear, particularly if the point corresponding to 180 ml. of fluid is ignored (Fig. 3), and the two quantities are highly correlated ($r=0.914$).

If y = the volume of amniotic fluid in ml.

$$x_1 = \frac{(\text{C.R. length in mm.})^3}{10^4}$$

and x_2 = the volume of the foetus in ml., then the quantities x_1 and x_2 are highly correlated ($r=0.902$) and are almost equal in value. Various regressions were tried, the success of any one being measured by the sum of the squared residuals (denoted by M), where each residual is the difference between an observed volume of fluid and a predicted value computed from the regression; the goodness of fit increases as M

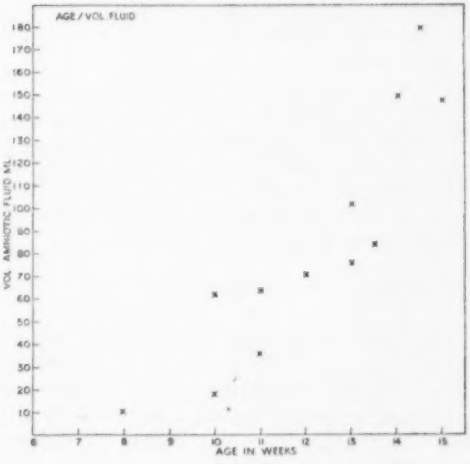

FIG. 2

Graph showing the relationship between volume of liquor amnii and age of the foetus during the first 15 weeks of pregnancy. As may be expected from Fig. 1, the graph is curved.

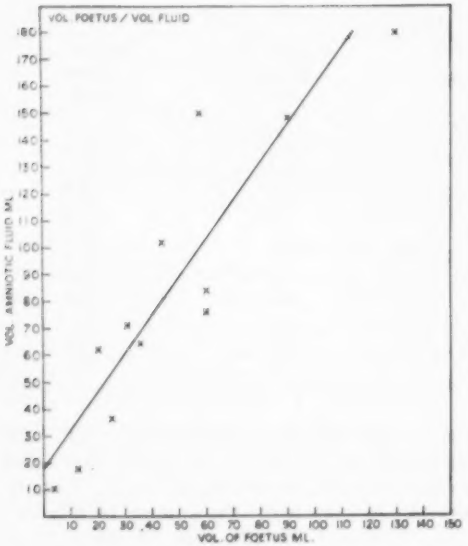

FIG. 3

Graph showing the relationship between the volume of liquor amnii and the volume of the foetus in the first 15 weeks of pregnancy. The regression line on the graph is indicated by the formula $y=1.366x+18.43$.

decreases. The results are as follows:

(1) y on x_2 alone: $M = 5552$
(2) y on x_1 alone: $M = 5056$
(3) y on x_2 and x_2^2: $M = 4771$
(4) y on x_1 and x_2: $M = 3961$

Denoting by y^* the predicted value,

$$y^* = 13.6 + 0.873x_1 + 0.650x_2$$

The difference between y and y^* varies from -22 to $+25$, the predicted value being mostly within about 20 ml. of the observed.

(4) *Volume of Liquor Amnii and Foetal Weight*

As would be expected from the fact that the specific gravity of the foetus remains constant, the correlation between the volume of liquor and the foetal weight is likewise linear (Fig. 4), and the measurements are highly correlated ($r=0.911$).

(5) *Volume of Liquor Amnii and C.R. Length cubed*

A similar linear relationship is obtained when the volume of the liquor is plotted against the cube of the C.R. length (Fig. 5), since the two quantities involved are in the same units.

(6) *Volume of Liquor Amnii and Surface Area of Foetus*

In view of the possibility that the liquor amnii may be derived from the foetal skin the relationship between the volume of the liquor and the surface area of the foetus was determined. The foetus *in utero* may be considered as a prolate spheroid or ellipsoid, i.e., the solid of revolution generated by the rotation of an ellipse about its major axis (Feldman, 1935). The volume of a prolate spheroid whose major axis $= 2a$, and whose minor axis $= 2b$, is represented by the formula $4/3\pi b^2 a$. In each set of observations taken in this investigation, a is known from the C.R. measurement, and the volume of the foetus was estimated in each case. It is therefore possible to calculate b for each foetus. From such measurements it is possible to calculate the surface area of each foetus from the formula:

$$\text{Surface area} = 2ab\left(\frac{\sin^{-1}e}{e} + \sqrt{1-e}\right)$$

where e = the eccentricity, which $= \sqrt{1-\frac{b}{a}}$

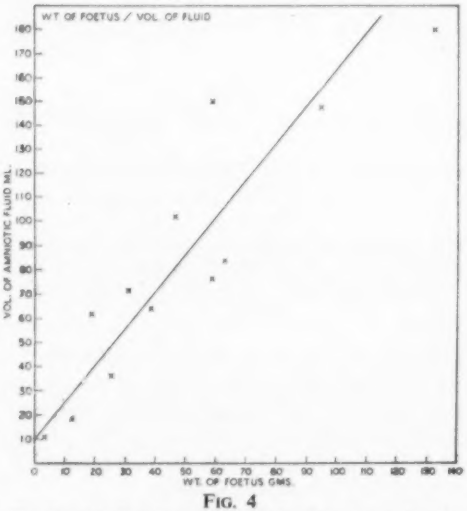

FIG. 4

Graph showing the relationship between volume of liquor amnii and weight of the foetus during the first 15 weeks of pregnancy. The regression line on the graph is indicated by the formula $y=1.328x+9.3$.

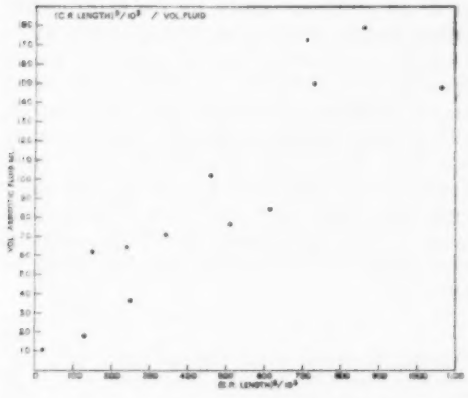

FIG. 5

Graph showing the relationship between volume of liquor amnii and C.R. length cubed in the first 15 weeks of pregnancy. The relationship is clearly linear.

The values of *a*, *b*, *e* and surface area of the foetus are given in Table II.

The graph showing the relationship between surface area of the foetus and volume of amniotic fluid is shown in Fig. 6. The relationship is linear and highly correlated ($r=0.991$). This does not imply a causal relationship between the two factors, but the linear relationship does demonstrate clearly that the volume of amniotic fluid increases *pari passu* with increasing surface area of the foetus during the period under investigation.

(7) *Relationship between Foetal Volume and C.R. Length*

As would be expected the relationship between the volume of the foetus and the C.R. length is curved (Fig. 7).

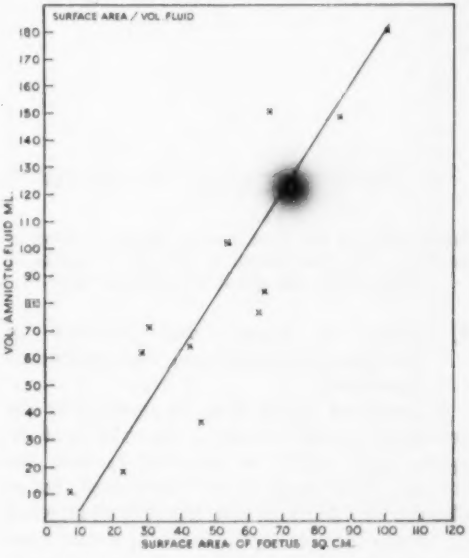

FIG. 6

Graph showing the relationship between volume of liquor amnii and surface area of the foetus in the first 15 weeks of pregnancy. The regression line on the graph is indicated by the formula $y=0.0193x-15.89$.

TABLE II

a in mm.	Volume of foetus in ml.	*b* in mm.	*e*	$\sin^{-1} e$	Surface area in sq. mm.
51.0	90	20.8	0.834	0.977	8960
14.0	3.5	7.7	0.698	0.768	898
25.5	12	10.6	0.827	0.960	2273
31.5	25	13.9	0.805	0.925	4617
35.0	15.5	10.1	0.917	1.152	3068
38.5	44	16.7	0.812	0.943	5435
26.5	20	13.2	0.752	0.838	2904
40.0	60	18.9	0.777	0.890	6381
42.5	60	18.0	0.821	0.960	6486
47.5	130	25.6	0.710	0.785	10149
31.0	36	16.7	0.710	0.785	4321
45.0	58	17.3	0.852	1.012	6620

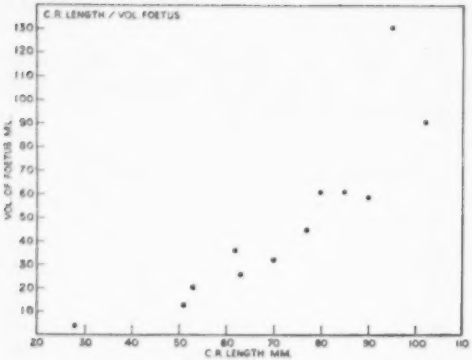

FIG. 7
Graph showing the relationship between volume of the foetus and C.R. length in the first 15 weeks of pregnancy. The graph is clearly curved.

(8) *Volume of Liquor and Duration of Pregnancy* (Authors' and Vonnegut's data combined)

A combined graph (Fig. 8) shows that the more rapid rate of increase in the volume of the liquor amnii which we observed between the 13th and 15th weeks is not maintained, but is followed by a decrease until the 26th week, when the volume increases again, reaching a maximum at approximately the 30th week of pregnancy. Thereafter there is a decrease until term. This terminal decrease was also noted by Haidlen (1887). Despite the fluctuations in the liquor volume the correlation between the crown-rump length and the volume of the liquor seems significant ($r = 0.658$), when the combined data are analyzed.

(9) *Volume of Liquor and Weight of Foetus* (Authors' and Vonnegut's data combined)

In Fig. 9 the volume of the liquor is correlated with the weight of the foetus. This graph supplements the results of Fig. 8, showing that the rate of increase in the volume of the liquor is greater after the foetus reaches 150 g. in weight and that after a foetal weight of 300 to 400 g. there is a decrease in the volume of the liquor amnii.

ARITHMETICAL CHECK

In view of the high degree of significance in the foregoing correlations it seemed desirable to make an arithmetic check on the experimental measurements in one case. The specimen was a 14-week gravid uterus removed entire by a total hysterectomy. It is known that the gravid uterus may be regarded as a prolate spheroid (Feldman, 1935), whose volume is expressed by the formula $4/3\pi b^2 a$. The major axis of the uterus from fundus to the internal os was 11 cm., the maximum transverse axis was 9 cm. The formula gives a calculated volume of 467 ml. Various experimental measurements were then made, as follows:

	ml.
Volume of blood which drained from the uterine vessels on removing haemostats ...	70
Volume of amniotic fluid	150
Volume of foetus as estimated by water displacement	58
Volume of uterus and placenta as estimated by Archimedes' principle after removal of foetus and amniotic fluid	245
Total	523

These measurements do not show great discrepancy, particularly if it is remembered that the volume of blood draining from the uterine vessels may not be a true index of the total amount in the uterus and placenta *in vivo*. The myometrium contracts with increasing force during the course of a hysterectomy, as can be demonstrated by the measurement of intra-amniotic pressure during the operation. At the onset of this operation the pressure within the amniotic sac was found to be 4 to 5 cm. of amniotic fluid, while at the termination of the operation the pressure had risen to 13 cm. of amniotic fluid. Upon incising the uterus after its removal from the abdomen, the uterus contracted much more forcibly and its wall became much thicker. This is evidenced by the great discrepancy between the volume of the lumen of the uterus (57 ml.) calculated arithmetically by Feldman's formula, and the volume of amniotic fluid + volume of foetus (208 ml.) measured experimentally. In the arithmetical calculation the major axis of the lumen of the uterus was taken as the maximum length of the uterus less twice the thickness of the uterine wall as measured after incision (2×2 cm. including decidua); the minor axis was calculated from the

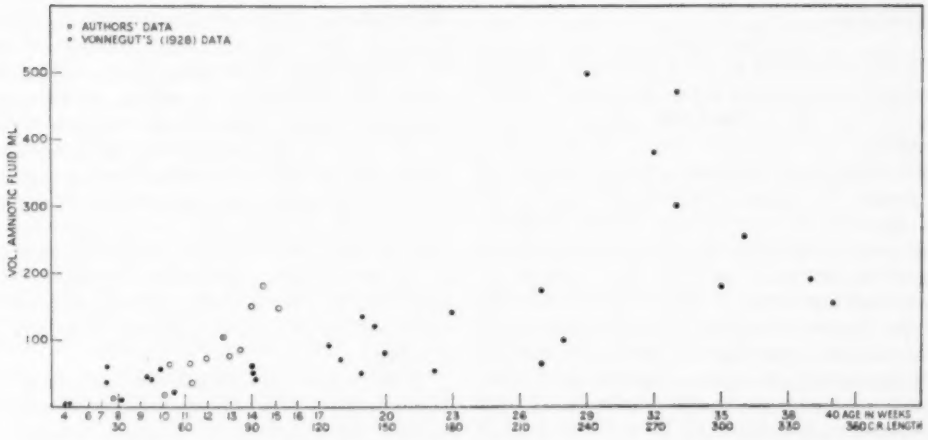

FIG. 8
Graph showing the relationship between volume of liquor amnii and age and C.R. length of the foetus throughout the whole course of pregnancy by the combination of the authors' data with those of Vonnegut (1928).

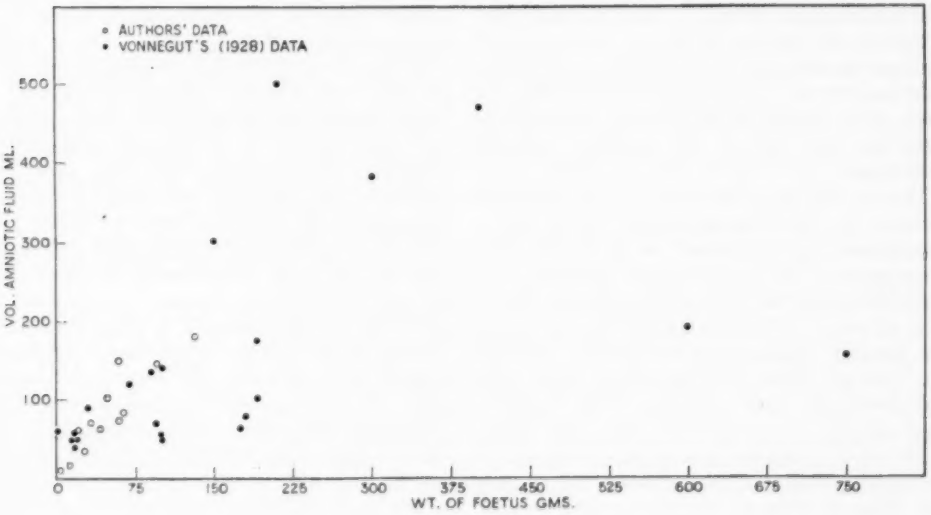

FIG. 9
Graph showing the relationship between volume of liquor amnii and weight of the foetus throughout the course of pregnancy by the combination of the authors' and Vonnegut's (1928) data.

maximum breadth of the uterus less twice the thickness of the uterine wall + the thickness of the placenta.

Discussion

In any discussion of the significance of these findings two questions are to be borne in mind, one the function of the liquor amnii, the other its origin.

The significant correlations found in the first 15 weeks of pregnancy between the volume of the liquor amnii and various foetal measurements show that the rate of secretion of the liquor is orderly, and that its amount is co-ordinated with the growth of the foetus. The graphs, liquor volume–foetal length, and liquor volume–foetal age (Figs. 1 and 2) are curved. In other words, the production of the liquor, though related to the foetal age, is not directly proportional arithmetically to it. The curved manner of this temporal increase in volume of liquor amnii when compared with the graphs, liquor volume–foetal volume, liquor volume–foetal weight, liquor volume–foetal surface area (Figs. 3, 4 and 6) in which the relationship is seen to be linear, suggests that the increase in liquor volume during this period is anticipatory. The linear nature of Figs. 3, 4 and 6 means that in the first 15 weeks of pregnancy the volume of the liquor is maintained so as to constitute about two-thirds of the conceptus volume (see Fig. 3, where $y = 1.366x + 18.43$). In other words there is maintained a constant relative hydramnios.

This physiological hydramnios is in excess of the amount which would be required to allow free expansion and movement to the foetus. The linear nature of the liquor volume–foetal volume graph compared with the curved growth graph suggests that the function of the liquor during this phase of pregnancy is to provide a distension growth stimulus to the uterus until such time as the increase in volume of the foetus is itself adequate to take over this function. There is, moreover, a general correspondence between the graph obtained by combining our results with those of Vonnegut (1928), and the graphs recorded by Needham (1931) collated from the results of various workers on liquor volume in domestic animals. Such a view harmonizes with Reynolds' (1949) concept of the function of the liquor in the rabbit. It would seem likely that some time between the 16th and the 20th week of pregnancy foetal growth reaches a critical point at which this particular function of the liquor becomes of lesser importance. During the phase of pregnancy in which spontaneous abortion is most common the volume of the liquor amnii is the dominant growth stimulus. Stated otherwise, the function of the liquor amnii is to provide an orderly and progressive distension stimulus in anticipation of the room needed later by the foetus. If this is so then the immediate cause of some spontaneous abortions, in a large number of which no gross cause can be discerned, may be a lag in the rate of formation of liquor.

There is another aspect of the problem of the liquor amnii which also required consideration, namely the relationship between volume of liquor and the tonus of the uterus. When the pregnant uterus is exposed and stimulated, rhythmic contractions are seen to sweep over it. These are transient, but if the uterus is handled, or if a spinal anaesthetic is administered (Malpas, 1944) the contractions become sustained. During these contractions the intra-uterine tension rises, as has been pointed out earlier, from a pressure of 4 cm. of liquor to a height of 13 cm. or so after a latent period of about 3 minutes. This is about the time it takes for a contraction elicited locally to spread and involve the whole uterus. If the amnion is intact the pressure then slowly falls, but if the amnion is pierced by any instrument wider than a fine bore manometer, the pressure, after an initial fall, then rises steadily, remains high, and the uterine wall rapidly and progressively retracts and thickens as the liquor escapes. The rapidity of the change in uterine tonus is most noticeable. The myometrium is, as it were, ready to contract immediately whenever the conceptus volume falls. This is readily demonstrated in any abdominal hysterotomy. On commencing the uterine incision the thickness of the uterine wall may be only 0.5 cm. The moment the last few muscle fibres are divided, the amnion bulges into the incision, and as the amnion is extruded the uterine wall immediately thickens to 2 to 3 cm. as the fibres shorten. There is, at the same time, some lateral retraction of the fibres away from

the incision, masking the total effect. The function of the liquor must be to ensure that the contractions of the uterus remain isometric; in other words, it would seem that uterine inhibition, upon which the continuance of pregnancy depends, may be mechanical, either wholly or in part. Such a view, perhaps a rather obvious one, is a natural corollary to the view that the prime function of the liquor is to provide a distension growth stimulus.

The Origin of the Liquor Amnii

The origin of the liquor amnii has been investigated by many workers (summarized by Needham, 1931). The human evidence is summarized by Shaw and Marriott (1949). Most, if not all, of the inquiries have been inconclusive. To use Aristotelian phraseology, these results may have been inconclusive because attention has been concentrated upon the immediate origin of the liquor rather than upon its final cause, that for which it exists. The correlations recorded in the present investigation suggest that it is produced in response to the need of the foetus for an adequate uterine capacity, and it seems a reasonable hypothesis that the foetus, if it does not secrete the liquor, does control its volume.

The linear correlation between the volume of the liquor and the surface area of the foetus is interesting and might be interpreted as some evidence that the liquor is derived from the foetal skin. The foetal epidermis is relatively undifferentiated in the first half of pregnancy, vernix caseosa not appearing until about the 24th week; there is therefore no histological objection to such a view of the origin of the liquor.

At best the course of a spontaneous abortion is a matter of speculation, but if the foregoing views have any substance the sequence of changes may be as follows. Impairment or faulty development of the foetus leads first to a lag in the secretion of liquor amnii, later to an absolute decrease in its volume. As a result there is first a failure of the distension growth stimulus. As the liquor then diminishes in volume, it fails in its secondary capacity as an inhibitor of uterine contractions. The uterine muscle then progressively contracts and retracts, and the intra-uterine pressure rises. The build up of uterine retraction proceeds until a critical point is reached, a level of tension at which the internal os is opened and the abortion becomes inevitable.

Summary

Study of the curves obtained by correlating the volume of the liquor amnii with various foetal measurements lends support to the view that the function of the liquor is not only to provide a fluid environment for the foetus, but also to provide a distension growth stimulus to the uterus in anticipation of the need for room for the growing foetus, and conversely to share in the maintenance of uterine inhibition, so that at all times during a continuing pregnancy the uterine contractions remain isometric.

The production of the liquor amnii is related intimately to the growth of the foetus, and the positive linear correlation between its volume and the surface area of the foetus certainly does not rule out the possibility that it is produced directly by the foetal skin.

These observations may have some bearing on the changes that take place in a spontaneous abortion.

We wish to thank Mr. R. L. Plackett for his assistance with the statistical analysis of the liquor volume–foetal volume relationships. We are also grateful to Mr. J. Hamilton and Mr. H. V. Corbett for the provision of some of the material.

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THE PLACENTAL CONCENTRATION OF CHORIONIC GONADOTROPHIN IN NORMAL AND ABNORMAL PREGNANCY

BY

J. A. LORAINE, M.B., Ph.D., M.R.C.P.

AND

G. DOUGLAS MATTHEW, M.B., F.R.C.S., F.R.C.O.G.

The Clinical Endocrinology Research Unit (Medical Research Council) and the Department of Obstetrics and Gynaecology University of Edinburgh

THE urinary excretion and serum concentration of chorionic gonadotrophin (C.G.) in normal and abnormal pregnancy have been studied by many workers in the past two decades and many methods of bioassay of C.G. have been employed. Originally investigators expressed results in terms of "rat" and "mouse" units (Smith and Smith, 1934; Cole and Saunders, 1935; Evans, Kohls and Wonder, 1937; Browne, Henry and Venning, 1939). More recently the introduction of an international standard for C.G. has made it possible to calculate results in international units. Estimations of the serum concentration of C.G. during normal pregnancy (I.U./litre) have been made by Jones, Delfs and Stran (1944), Wilson, Albert and Randall (1949), Haskins and Sherman (1952) and Loraine and Matthew (1953), while the urinary excretion (I.U./24 hours) has been studied by Loraine (1950a) and by Albert and Berkson (1951).

Using the method of assay for C.G. depending on the increase in prostatic weight in immature rats (Loraine, 1950a), it has been shown that the curve for the urinary excretion of C.G. during normal pregnancy has two distinct phases. During the first trimester of pregnancy high readings (20,000–50,000 I.U./24 hours) are obtained and there is much individual variation from one patient to another. This constitutes the so-called "peak phase" of C.G. excretion. In the second and third trimesters the excretion is relatively more constant and during this period the normal range ($P=0.99$) is approximately 4,000–11,000 I.U./24 hours. These estimations of the urinary C.G. are quantitatively very similar to those for the serum concentration expressed in I.U./litre and it has been concluded that during the last two trimesters of pregnancy urinary and serum levels of C.G. consistently above 11,000 I.U. must be considered abnormal. Such abnormally high figures are found in a proportion of pregnant diabetic women (Loraine, 1949) and in some severe cases of pre-eclamptic toxaemia (Loraine and Matthew, 1950).

The elegant experiments of Jones, Gey and Gey (1943) and of Stewart, Sano and Montgomery (1948) demonstrated that C.G. is produced *in vitro* in placental tissue culture. This property was most marked in the Langhans cells which may retain this capacity for up to 6 months. Bruner (1951), estimating vaginal cornification in rats to assay C.G., studied the distribution of the gonadotrophin in mother and foetus at different stages of normal pregnancy. It was shown that the concentration of C.G. was maximal in the chorionic area of the placenta and that the pattern of distribution of the gonadotrophin was in keeping with the assumption that the chorion releases C.G. into the maternal circulation.

There are in the literature, however, few quantitative estimations of placental concentration of C.G. under normal and abnormal conditions. Smith and Smith (1935) estimated the C.G. content of placentae from 10 normally pregnant women, 8 patients with pre-eclamptic toxaemia and 5 eclamptics. It was found that placentae from pre-eclamptic and eclamptic patients contained a significantly greater concentration of C.G. than those from normally

pregnant women. Results were expressed in " rat units ", corpora lutea in the ovary forming the end-point of the assay. Various workers, including Augustin (1941) and Bickenbach (1941), have demonstrated a considerably higher concentration of C.G. (" Units "/g.) in placentae obtained during the early weeks of gestation as compared with those examined in late pregnancy. By far the most careful and detailed study of the C.G. concentration in normal human placentae is that of Diczfalusy (1953). This worker, who expressed results in international units, estimated the C.G. content of 40 placentae at various stages of normal pregnancy. Two different assay methods for C.G. were employed, one depending on the increased weight of the accessory sex organs in immature male rats and the other based on the formation of corpora lutea in the ovaries of immature mice. Great attention was given to the problem of assay design and the results were subjected to careful statistical analysis. It was found that the placental C.G. concentration (I.U./g. wet weight) was maximal in the second and third months of pregnancy (corresponding to the peak period in blood and urine), fell rapidly in the third and fourth months, and from the fifth month until term was relatively constant, remaining below 20 I.U./g.

The present study comprises the estimation of placental C.G. concentration in 27 patients who had uncomplicated pregnancies with vaginal deliveries, 12 patients delivered by Caesarean section for purely obstetrical indications, 17 cases of pre-eclamptic toxaemia, 14 pregnant diabetic women and 11 patients in whom various other complications occurred during pregnancy. The pre-eclamptic cases were classified on a clinical basis into three categories—mild, moderate and severe. Criteria for the classification are described elsewhere (Loraine and Matthew, 1950). In a small number of subjects the serum C.G. was also estimated during labour.

Methods

(*a*) *Method of extraction of placental C.G.*

The technique employed was similar to that used by Kapeller-Adler (1952) for the extraction of histaminase from placental tissue. The placenta was obtained immediately after delivery and extraction was performed on the same day. Superficial blood was removed by rapid rinsing with cold water and by thorough blotting between sheets of filter paper. Great care was taken to avoid possible contamination of the placental extract by maternal blood. After removal of the membranes and umbilical cord the organ was weighed. The whole placenta was then homogenized either by grinding in a mortar or by mincing in an electric mincing apparatus. 20 g. of the thoroughly mixed pulp was ground in a mortar with 20 ml. 0.9 per cent saline for approximately 15 minutes. The aqueous extract was centrifuged for 30 minutes at 2,000 r.p.m. and the supernatant fluid decanted and stored in the refrigerator during the 3-day injection period required for the assay. Evidence has been obtained that placental extracts prepared in this way show no diminution of C.G. activity over a period of approximately two weeks provided adequate refrigeration is undertaken.

It has also been established that the yield of C.G. from placental tissue is not significantly increased when repeated extraction with saline is employed. Comparison of the yields (single versus repeated extraction) has been made in a placenta obtained by Caesarean section from a patient at 40 weeks gestation. The design of the experiment was as follows: 20 g. of placental tissue was extracted 4 times with 10 ml. quantities of 0.9 per cent saline. The residue was centrifuged down after each extraction and the extracts combined. Each of 6 rats received a total dose equivalent to 0.5 g. placental tissue in divided doses over 3 days. The animals were killed on the fourth day, the prostates fixed in Bouin's solution for 24 hours and weighed on the fifth day. The mean prostatic weight in this group expressed as mg./100 g. rat weight was 137.

For injection into a second group of 6 rats only one extraction with saline of the same placenta was made. Again each animal received a total dose equivalent to 0.5 g. placental tissue and the injection schedule employed was as described above. The mean prostatic weight (mg./100 g. rat weight) was 134. Since the

TABLE I

Comparison of the Yields of C.G. from Placentae using Different Methods of Preparation

Patient	Duration of gestation, weeks	Mode of delivery	Placental weight, g.	Method of extraction	Number of rats per group	Total loss of placenta per rat, g. wet weight	Mean prostatic weight, mg./100 g. rat weight	Placental C.G. concentration I.U./g. wet weight	Serum C.G. I.U./ml.
1	32	Vaginal	352	Saline	5	0.6	130	3.73	—
				Lyophilization and saline	5	≡0.6	140	4.09	
2	40	Vaginal	535	Saline	5	0.8	168	4.54	—
				Lyophilization and saline	5	≡0.8	173	4.69	
3	42	Vaginal	500	Saline	5	0.4	123	5.00	—
				Lyophilization and saline	5	≡0.4	120	4.87	
4	42	Vaginal	365	Saline	5	0.8	154	3.78	—
				Lyophilization and saline	5	≡0.8	156	3.86	
5	40	Vaginal	520	Saline	6	0.5	120	4.48	4.67
				Acetone	6	≡0.5	125	4.80	
6	40	Caesarean section	438	Saline	6	0.5	134	5.50	5.90
				Acetone	6	≡0.5	132	5.26	
7	40	Vaginal	448	Saline	6	0.5	137	5.76	6.18
				Acetone	6	≡0.5	132	5.26	

results in the two groups are not significantly different, it can be concluded that the yield of C.G. from placental tissue is not significantly increased by repeated saline extraction.

The yield of C.G. with the saline extraction technique outlined above has been compared with that obtained by methods involving:

(i) *Lyophilization of placental tissue with subsequent saline extraction.* Comparisons were made in 4 normal placentae (Table I). 20 g. of placental tissue was first frozen, then lyophilized and ground to an homogeneous powder. Approximately 3 g. of this powder was extracted 4 times at room temperature with 5 ml. quantities of 0.9 per cent saline. The residue was centrifuged down after each extraction and the extracts combined.

(ii) *Extraction with phosphate buffer at pH* 7.8 *followed by precipitation by* 8 *volumes of acetone at pH* 4.0. This is the technique adopted by Diczfalusy (1953) who states that the extraction method yields approximately 95 per cent of the total C.G. activity. Comparisons were made in 3 placentae and the results are shown in Table I. The average quantitative yields of the lyophilization and acetone precipitation techniques when compared with the aqueous extraction method were 103.1 per cent and 98.2 per cent respectively. It can therefore be concluded that results obtained by all three methods are comparable. Because of its simplicity, extraction by saline alone would seem to be the method of choice. In 3 patients the serum C.G. concentration was estimated during labour. It will be noted (Table I) that the serum concentration (I.U./ml.) was almost exactly equal to the placental C.G. concentration (I.U./g. wet weight).

(*b*) *Method of assay of C.G.*

This depends on the increase in weight of the prostate in intact immature rats. Assays are made in comparison with the international standard for C.G. The technique is fully described in a previous paper (Loraine, 1950a).

Since the international standard was prepared from pregnancy *urine*, it is theoretically possible either that placental C.G. might differ qualitatively from urinary C.G. or that placental extracts might contain augmenting or inhibiting substances interfering with the response of the prostate to C.G. When a 4-point assay design (2 doses of the standard versus 2 doses of the unknown) was employed, however, no significant deviation from parallelism was found. This is in keeping with the observations of Diczfalusy (1953). It was therefore considered justifiable to use as a routine the asymmetrical 3-point design in which 2 doses of the standard and 1 dose of the extract were administered. Previous experience had shown that the effect of the standard preparation on the prostates showed little variation in our rats, and therefore assays were made in comparison with the standard at intervals of approximately 1 month.

Results

These are presented in summary form in Table II. Owing to the rather wide variation in the placental C.G. concentrations the significance of the results has been tested in the following way as recommended by Gaddum (1945). Each estimate was converted to a logarithm. The mean and standard deviation of each group of logarithms was then calculated. Column 3 gives the concentration of C.G. corresponding to the mean of the logarithms in each group and is thus the geometric mean of the observations. Column 4 gives the standard deviation of the logarithms. The figures in Column 5 are derived from those in Column 4 and give the range within which it is expected that 95 per cent of the results will lie.

It was found that the mean figure for placental C.G. concentration in patients with uncomplicated pregnancy and vaginal delivery (Table III and Fig. 1) did not differ significantly ($P = 0.6$–0.7) from that obtained in cases of Caesarean section for obstetrical indications (Table IV and Fig. 2).

Since both methods of delivery were employed in the toxaemic and diabetic groups it was considered advisable to combine the groups consisting of normal vaginal deliveries and Caesarean section for other obstetrical indications, for the purpose of providing a comparable control series when calculating the significance of results in the abnormal groups.

TABLE II
Placental C.G. Concentration in Normal and Abnormal Pregnancy

Type of case	Number of patients	Mean C.G. concentration (I.U./g. wet weight)	Standard deviation of the logarithm	Range (P=0.95) (I.U./g. wet weight)
Uncomplicated pregnancy with vaginal delivery	27	4.11	0.12	2.39 to 7.06
Caesarean section (obstetrical abnormalities)	12	4.28	0.13	2.39 to 7.73
Vaginal delivery and Caesarean section	39	4.17	0.12	2.43 to 7.16
Toxaemia (mild, moderate, and severe cases)	17	5.97	0.15	3.03 to 11.75
Mild toxaemia	3	5.11	0.23	3.03 to 14.39
Moderate toxaemia	8	5.70	0.11	3.44 to 9.33
Severe toxaemia and eclampsia	6	6.89	0.16	3.34 to 14.19
Diabetes mellitus	14	5.16	0.22	1.92 to 13.93
Complicated pregnancy from 29th week	8	4.72	0.11	2.87 to 7.76

TABLE III
Uncomplicated Pregnancy with Vaginal Delivery

Serial No.	Age	Number of pregnancy	Gestation at delivery (weeks)	Placental weight (g.)	C.G. I.U./g. wet weight	Foetal weight pounds	ounces
1/1069	29	1st	40	323	6.18	5	10
2/1138	26	2nd	42	415	3.30	7	6
3/1195	19	1st	41	602	2.88	5	8
4/1198	24	2nd	43	733	3.09	10	4¾
5/1269	21	1st	40	567	4.50	7	9½
6/1289	23	1st	40	650	3.29	7	4½
7/1304	25	2nd	40	487	2.68	7	11
8/1390	22	1st	40	520	3.36	7	5
9/1458	23	1st	39	532	3.73	7	12¼
10/1522	26	3rd	40	534	4.54	8	13
11/1529	21	1st	40	495	4.54	7	5
12/1530	23	1st	42	500	3.61	8	2
13/1531	22	1st	42	365	3.78	6	12
14/1868	20	1st	38	343	4.91	6	4½
15/2090	24	1st	40	625	3.54	7	15
16/2125	28	2nd	41	462	4.38	7	6½
17/2262	29	1st	41	535	4.00	7	13
18/2287	34	1st	40	451	4.59	6	3¾
19/2327	19	1st	38	483	2.89	6	10½
20/2537	27	5th	40	1050	5.90	11	15
21/2746	20	1st	42	403	6.77	8	5
22/3103	19	1st	43	540	5.28	9	3½
23/3113	21	3rd	41	398	3.64	6	2½
24/3129	21	2nd	40	433	3.03	7	1½
25/3218	30	3rd	41	490	8.18	7	14
26/3294	24	2nd	40	753	5.27	8	10½
27/3316	22	1st	41	510	4.09	7	11½
28/3394	21	1st	40	434	4.43	7	11½

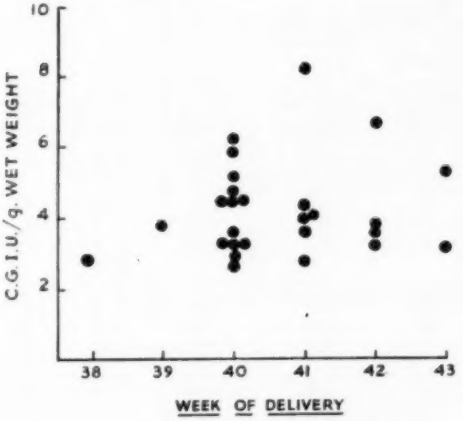

FIG. 1
Uncomplicated pregnancy with vaginal delivery

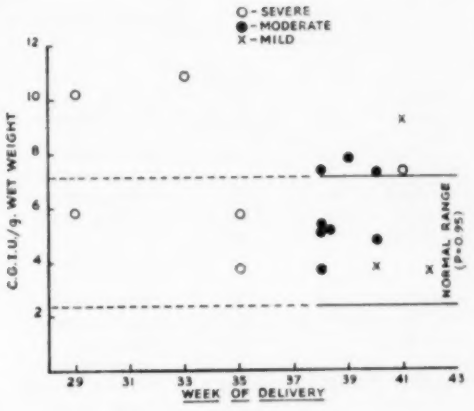

FIG. 3
Toxaemia

In the 17 patients with pre-eclamptic toxaemia (Table V and Fig. 3) the mean placental C.G. concentration was significantly higher than that obtained in the control series ($P<0.001$). The pre-eclamptic patients were subdivided into 3 groups—mild, moderate and severe. In the mild cases the mean figure did not differ significantly from that in the control series ($P=0.2$–0.3) but in both the moderate and severe cases the mean placental C.G. concentration was significantly higher than that obtained in the control series ($P<0.01$ and <0.001 respectively). A similar significant difference was noted in the pregnant diabetic women ($P<0.01$). The results are presented in Table VI and Fig. 4.

FIG. 2
Caesarean section for obstetric complications

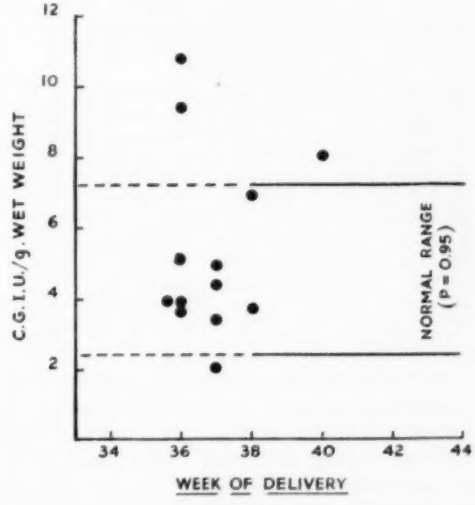

FIG. 4
Diabetes mellitus

TABLE IV
Caesarean Section for Obstetric Complications

Serial No.	Age	Number of pregnancy	Main indication	Gestation at delivery (weeks)	Placental weight (g.)	C.G. I.U./g. wet weight	Foetal weight pounds	ounces
1/1714	36	2nd	Disordered uterine action	39	291	5.20	6	1
2/2406	41	1st	Disproportion	40	633	5.47	10	4½
3/2643	37	2nd	Prolapsed cord	39	515	4.27	7	15
4/2778	36	4th	Previous Caesarean section	40	613	4.58	8	11½
5/2871	28	1st	Disproportion	42	638	5.63	8	0½
6/2910	37	3rd	Disproportion	40	418	4.48	6	5½
7/3022	37	7th	Recurrent abortion (6)	40	345	3.20	6	8½
8/3027	32	2nd	Placenta praevia	39	450	4.58	6	12
9/3068	35	2nd	Foetal distress	40	762	2.01	9	6½
10/3147	24	1st	Disproportion	40	303	4.42	6	11½
11/3353	24	1st	Disordered uterine action	40	491	5.41	6	14
12/3595	25	3rd	Disproportion	39	483	4.04	6	14¼

TABLE V
Toxaemia

Serial No.	Age	Number of pregnancy	Severity	Gestation at delivery (weeks)	Onset of labour	Placental weight (g)	C.G. I.U./g. wet weight	Foetal weight pounds	ounces
1/2908	27	1st	Mild	41	Spontaneous	576	9.31	9	2½
2/2729	37	2nd	Mild	40	Spontaneous	473	3.81	11	0
3/2745	35	2nd	Mild	43	Spontaneous	505	3.74	8	7¼
4/809	30	6th	Moderate	38	Caesarean section	488	3.75	8	2½
5/2093*	25	1st	Moderate	38	Spontaneous	435	5.38	6	0
						461	5.14	7	7
6/2149	34	1st	Moderate	39	Caesarean section	547	7.81	6	1¼
7/2679	39	4th	Moderate	38	Spontaneous	590	5.15	7	10
8/2705	21	1st	Moderate	40	Spontaneous	475	4.88	8	1
9/3300	30	1st	Moderate	40	Surgical induction	525	7.38	7	3
10/3419	36	1st	Moderate	40	Caesarean section	619	7.41	8	1¼
11/225	29	1st	Severe	29	Caesarean section	363	5.90	2	12½
12/1762	21	1st	Severe	29	Caesarean section	225	10.21	2	11¾
13/2087	23	1st	Severe	35	Surgical induction	440	5.78	4	8
14/3132	30	2nd	Severe	33	Surgical induction	485	10.78	3	14
15/3201	31	2nd	Severe	35	Surgical induction	203	3.90	3	13½
16/2220	23	1st	Eclampsia	41	Spontaneous	233	7.24	6	3

* Twin pregnancy.

In Table VII are shown the placental C.G. concentrations in a miscellaneous group of patients in whom various other complications occurred during pregnancy. The mean figure in these cases did not differ significantly from that in the control series ($P = 0.2$–0.3). Observations were made in 3 additional women in the first trimester of pregnancy. In 2 patients with cardiac disease delivered by abdominal hysterotomy at the 12th and 14th weeks the C.G. concentrations (I.U./g. wet weight) were 24.74 and 12.27 respectively. In the third case a spontaneous abortion occurred at the 13th week and the C.G. concentration was 9.84 I.U./g.

TABLE VI
Diabetes Mellitus

Serial number	Age	Number of pregnancy	Additional complications	Gestation at delivery (weeks)	Method of delivery	Placental weight (g.)	C.G. I.U./g. wet weight	Foetal weight pounds	Foetal weight ounces
1/19	27	2nd	Hydramnios: intra-uterine death	37	Caesarean section	313	3.35	6	3
2/62	24	1st	Hydramnios: intra-uterine death	36	Vaginal	517	3.99	8	2
3/214	33	3rd	———	36	Caesarean section	603	3.73	9	0
4/522	27	1st	———	36	Caesarean section	540	3.90	7	1
5/946	21	2nd	———	37	Caesarean section	540	2.00	6	9¼
6/1516	22	1st	Hydramnios	34	Caesarean section	480	11.72	10	10¼
7/1852	28	1st	Hydramnios	36	Caesarean section	519	5.03	8	1
8/1937	43	7th	Essential hypertension	38	Caesarean section	420	3.61	5	15
9/2130	31	4th	Hydramnios	36	Caesarean section	528	9.39	7	5½
10/2388	32	2nd	Hydramnios	40	Caesarean section	410	7.99	7	3½
11/2582	35	2nd	Hydramnios: essential hypertension	37	Caesarean section	488	4.38	5	14½
12/2799	20	1st	———	37	Caesarean section	443	4.70	7	10½
13/2947	38	11th	———	38	Vaginal	770	6.97	9	8
14/3171	37	2nd	Hydramnios	36	Caesarean section	380	10.78	7	4½

TABLE VII
Other Complications of Pregnancy

Serial number	Age	Number of pregnancy	Complication	Gestation at delivery (weeks)	Type of delivery	Placental weight (g.)	C.G. I.U/g. wet weight	Foetal weight pounds	Foetal weight ounces
1/2221	36	8th	Concealed accidental haemorrhage	38	Vaginal	440	5.78	7	8
2/2365	39	1st	Essential hypertension	43	Vaginal	320	4.78	6	8½
3/2929	27	2nd	Antepartum haemorrhage: intrapartum death	29	Vaginal	145	3.72	1	9
4/2933	36	4th	Essential hypertension	41	Caesarean section	618	4.38	9	3½
5/3035	25	3rd	Hydramnios: anencephaly	32	Vaginal	343	4.69	2	7
6/3230	35	6th	Combined accidental haemorrhage	35	Vaginal	300	5.91	4	11
7/3312	20	2nd	Hydramnios: anencephaly	34	Vaginal	415	6.50	2	13½
8/3669	30	2nd	Chronic nephritis	38	Caesarean section	477	3.03	7	4½

Discussion

In normal patients and in those delivered by Caesarean section for obstetric reasons the range for placental C.G. ($P=0.95$) lay between 2.43 and 7.16 I.U./g. wet weight (Table II). The figures for the range were compiled from data on placentae delivered from the 38th to the 43rd week of gestation (Figs. 1 and 2). In the toxaemic and diabetic patients, however, many placentae were obtained at a much earlier phase of gestation (Figs. 3 and 4). Nevertheless in calculating the significance of the results it was considered that it would be permissable to compare the concentrations in the normal with those in the abnormal conditions, although the gestation periods in the 2 groups were different. This conclusion was reached as a result of the work of Diczfalusy (1953) who, using a very similar assay method for C.G., demonstrated that the placental concentration of the hormone (I.U./g. wet weight) remained relatively constant from the 20th week of pregnancy until term.

The close similarity between the results of the serum concentration of C.G. (I.U/ml.) and the placental concentration (I.U./g. wet weight) in both normal and abnormal conditions suggests that the hormone is not stored in the placenta but is rapidly and continuously released into the general circulation. Abnormally high figures for the urinary excretion and serum concentration of C.G. have been reported in a proportion of cases of pre-eclamptic toxaemia (Smith and Smith, 1939; Watts and Adair, 1943; Loraine and Matthew, 1950) and in pregnant diabetics (White, 1949; Loraine, 1949). The present study has demonstrated that in these conditions the placental concentration of C.G. may be significantly higher than that in normal pregnancy.

At present little is known either of the function of C.G. during gestation or of the mechanism whereby the relative constancy of the C.G. concentrations in the serum, urine and placenta is maintained during the last 2 trimesters of normal pregnancy. It has, however, been established (Gastineau, Albert and Randall, 1949; Loraine, 1950b) that the renal clearance of C.G. (ml./min.) remains constant during this period in normal and diabetic pregnancy. It seems possible that the production and utilization of the hormone also remain unchanged. There is at present no evidence to support the view of Smith and Smith (1939) that increased production of placental C.G. is paralleled by increased utilization of the hormone for the elaboration by the placenta of oestrogens and progesterone.

Summary

(1) Studies of the placental concentration of C.G. (I.U./g. wet weight) have been made in 27 normally pregnant women delivered by the vaginal route, 12 patients delivered by Caesarean section for obstetric indications, 17 cases of pre-eclamptic toxaemia, 14 pregnant diabetic women and 11 patients in whom various other complications occurred during pregnancy. In all estimations the prostatic weight method of assay for C.G. was used.

(2) The placental C.G. concentration (I.U./g. wet weight) did not differ significantly between normal patients delivered by the vaginal route and cases delivered by Caesarean section for purely obstetric indications.

(3) In moderate and severe pre-eclamptic toxaemia and in diabetic pregnancy the mean figure for the C.G. concentration of the placenta was significantly higher than that in the control series. In mild pre-eclamptic toxaemia and otherwise complicated pregnancy, however, the mean figure did not differ significantly from that in the control series.

(4) A simple saline method of extraction appeared to give a satisfactory yield of placental C.G. when compared with techniques involving lyophilization and acetone precipitation.

(5) In a small number of cases the serum concentration of C.G. (I.U./ml.) was very similar to the placental concentration (I.U./g. wet weight).

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HEART DISEASE IN PREGNANCY

A Review of 228 Cases

BY

D. J. MACRAE, M.D., F.R.C.S., F.R.C.O.G.

Obstetrician, The Mothers' Hospital, London

Gynaecologist and Obstetrician, The North-West Metropolitan Hospitals, Watford

IN recent years there has been a marked fall in the maternal mortality. The number of maternal deaths which still occur from heart disease, however, shows this complication to occupy a more prominent place in mortality tables and in some obstetric centres to be the commonest cause. For this reason a series of 228 consecutive cases is presented, in which there was no maternal death.

Mendelson and Pardee (1942) were among the first to show that good antenatal care could achieve this end, when they recorded a series of 200 obstetric cases with heart disease without a single maternal death. The main emphasis in the management of their patients seemed to lie in the prevention of heart failure or the recognition of its earliest signs and their immediate treatment. With a similar end in view, in 1947, I set up for patients with heart disease a routine of obstetric care which I explained in the William Blair Bell Memorial Lecture of that year (MacRae, 1948). All cases were placed in one of the 4 groups of the American Heart Association classification. Patients of Groups 1 and 2 were accorded the care outlined below. The large majority of Groups 3 and 4 patients were, with rest and treatment, brought into Group 2; and for the few in early pregnancy who did not improve therapeutic abortion was considered.

RESULTS

Total number of cases	228
Maternal deaths	0
Number of abortions	11
Spontaneous — 4 (1.8 per cent)	
Therapeutic — 7 (3.2 per cent)	
Number of viable babies (2 sets of twins)	219
Stillbirths	5
Corrected to	2
Rate per 1,000 deliveries	9
Neonatal deaths	5
Corrected to	3
Rate per 1,000 live births	14

ANTENATAL CARE

The course of antenatal care given can briefly be summarized as follows:

(1) The maximum rest possible is advised, including rest in bed 2 hours in the afternoon and 10 hours at night.

(2) Daily exercise and work are performed within the limits of dyspnoea or tiredness.

(3) The daily activities of the patient are discussed with her and firm emphasis is given to the importance of adhering strictly to an agreed plan; and any departure such as house moving, long shopping expeditions, excess liberties at holiday times are avoided. In patients who are over 30 years of age a more restricted mode of living is advocated.

(4) Assistance from the Home Help Scheme is obtained, if necessary, to lighten the burden of household duties and shopping; and transport may be given to bring the patient to the clinic.

(5) The patient reports, if her progress is satisfactory, every fortnight during the first half of pregnancy, and weekly thereafter. This gives frequent opportunity to ensure that there is no deterioration in her health and, since cardiac decompensation can readily occur, permits early discovery of its signs such as an increase in pulse rate, breathlessness, cyanosis, cough after exertion. A special look-out is kept for the appearance at the lung bases of crepitations, which so often herald the onset of heart failure.

(6) The patient is advised on her diet during pregnancy and encouraged to take meat, fish, liver, fresh vegetables and vitamin tablets. Salt in cooked food is reduced and avoided at the table and fluids are taken in moderation—thirst being relieved mainly by fruit, to lessen the risk of water retention. The gain in weight must not exceed that of a normal pregnancy.

(7) Anaemia, which may precipitate heart failure, is avoided by taking ferrous sulphate daily and the patient's haemoglobin is checked by monthly estimations.

(8) The patient is warned to avoid chills and respiratory infections, since illnesses, even those trivial to healthy patients, can initiate heart failure. She is told to go to bed and to notify her doctor or the clinic at the slightest illness.

(9) Antibiotics are given if carious teeth are removed, to avoid the risk of subacute bacterial endocarditis.

(10) Special care is taken of the patient about the 28th week of pregnancy, when the strain on the heart has reached its maximum; and she may be admitted for a week's rest and observation if her progress is in doubt.

(11) Patients who have a persistent cough, blood-stained sputum, persistently rapid pulse, or show signs of cardiac decompensation, are admitted to hospital where they may remain until term.

(12) All patients are admitted 7–10 days before delivery for complete rest and reassurance.

Therapeutic Abortion

Termination of pregnancy was performed in 7 patients, 3.2 per cent, of the series. Three of the patients had mitral stenosis and aortic regurgitation, two of whom remained in Group 4 and the other in Group 3 after a period of rest and treatment. Another patient in Group 3 had auricular fibrillation, which carries a bad prognosis. Three were Group 2 patients, one of whom, a gravida–3, had aortic regurgitation and, as is common with this lesion, was difficult to control; while 2 patients, aged 35 and 41 years respectively, had each 4 children and a history of previous heart failure.

A few Group 3 patients were, with extra rest and care, safely carried throughout their pregnancy. In some cases in this group the decision to take this course was helped by a consideration of the aetiology, duration and severity of the lesion and the increase in size of the heart; and an appreciation of the progressive and fatal course of rheumatic heart disease.

Temporary cardiac decompensation, with a change from Group 2 to the unfavourable Groups 3 and 4, occurred in about 15 per cent of this series. This was mainly due to respiratory infections, anaemia, and physical exhaustion in some instances associated with holidays. A few patients were first seen late in pregnancy and remained in Group 3.

There were 4 spontaneouss abortions, 2 in Group 2 patients with mitral stenosis, and 2 in Group 3 patients, one of whom had mitral stenosis and the other, calcified pericarditis and mitral stenosis.

Table I

Functional group of patients at time of delivery or abortion

Group	Number	Per cent
1	86	38.2
2	111	48.7
3	28	11.8
4	3	1.3
Total	228	100.0

Table II

Types of heart lesion

Mitral stenosis with or without regurgitation ...	192
Mitral stenosis and aortic regurgitation	15
Aortic stenosis	1
Aortic regurgitation	2
Myocarditis and tachycardia	1
Congenital	17
Total	228

Of the 17 patients with congenital heart disease the exact nature of the lesion was uncertain in 4, in 6 there was a patent interventricular septum, 4 had pulmonary stenosis and 2 a patent ductus arteriosus, while 1 had a coarction of the aorta for which a Caesarean section was performed. There were 2 other Caesarean deliveries in this group but the remainder were delivered normally.

The incidence of congenital heart disease in this series is high, but is probably accounted for by the fact that many patients with heart lesions were especially referred to the hospital. There were no stillbirths in this group, but there were 2 neonatal deaths, both associated with spontaneous, premature rupture of membranes and deliveries at 30 and 28 weeks respectively, in patients with congenital pulmonary stenosis.

TABLE III

Type of lesion and functional group

Lesion	Group				
	1	2	3	4	Total
Mitral stenosis with or without regurgitation	73	95	23	1	192
Mitral stenosis and aortic regurgitation	–	11	2	2	15
Aortic stenosis	1	–	–	–	1
Aortic regurgitation	1	1	–	–	2
Myocarditis and tachycardia	–	1	–	–	1
Congenital	11	3	3	–	17
Total	86	111	28	3	228

TABLE IV

Functional group in relation to gravidity in mitral stenosis cases

	Gravid										
	1		2		3		4		4+		
Group	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	Total
1	45	45	19	34.6	6	30	2	15.4	1	14.3	73
2	46	46	27	53.9	11	55	7	53.8	4	57.1	95
3	8	8	6	11.5	3	15	4	30.8	2	28.6	23
4	1	1	–	–	–	–	–	–	–	–	1
Total	100	100.0	52	100.0	20	100.0	13	100.0	7	100.0	192

TABLE V

Functional group in relation to age in mitral stenosis cases

	Age										
	Under 20		20–24		25–29		30–34		35 and over		
Group	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	Total
1	1	25	43	51.2	22	31.3	18	37.0	9	28.1	73
2	3	75	17	39.5	36	53.7	25	54.3	14	43.8	95
3	–	–	3	9.3	9	15.0	2	6.5	9	28.1	23
4	–	–	–	–	–	–	1	2.2	–	–	1
Total	4	100.0	43	100.0	67	100.0	46	100.0	32	100.0	192

A definite history of rheumatic fever was obtained from 87 per cent of the remaining 211. If the lesion at the mitral valve alone is considered, there were 192 patients involved and Table IV shows that there were fewer patients in Group 1 and more in Group 3 as the gravidity increased beyond 3; while Table V reveals that in patients over 35 years of age a higher proportion were in Group 3.

CARE DURING LABOUR

The patient approaches her confinement with rest and reassurance in hospital 7–10 days before delivery and with the view that a normal labour can be achieved. During labour special care is taken to ensure that sedation and nutrition are adequate and the response of the heart is checked by an hourly pulse chart and a close watch for cyanosis or dyspnoea. In no instance in this

series was digitalization of the heart necessary during labour; any increase in pulse rate was associated with too much pain or anxiety, and for this morphia, gr. ¼, was found to be the best drug. When further sedation was necessary pethidine, either alone or with potassium bromide or seconal, was given.

For the second stage of labour the analgesic was gas and air, or gas and oxygen if cyanosis were present. A perineal and pudendal block with 1 per cent Novocaine was performed in most cases and, when delay was present, the delivery of the child was assisted by an episiotomy or forceps; the forceps rate of 19.3 per cent showed that assistance was not often necessary.

The third stage of labour was conducted by a doctor in the same way as for normal patients. When the placenta had separated it was expelled by the patient during a contraction of the uterus, or with the help of a little suprapubic pressure. A little blood loss at this stage can be of benefit to the patient, but mismanagement such as is associated with too early, or repeated attempts to expel the placenta can lead to severe haemorrhage and shock. To perform a manual removal of the placenta in patients with heart disease is to court disaster.

Omitting the cases of congenital heart lesion and the abortions, the remaining 200 patients (2 sets of twins) were delivered as follows:

TABLE VI

Mode of delivery

	Number	per cent
Normal	151	74.7
Forceps	39	19.3
Breech	4	2.0
Caesarean section	8	4.0
Total	202	100.0

TABLE VII

Type of delivery in relation to functional group

Group	Normal	Forceps	Caesarean	Breech	Total
1	61	11	2	1	75
2	79	21	3	2	105
3	11	6	3	1	21
4	–	1	–	–	1
Total	151	39	8	4	202

CAESAREAN SECTION

This operation was found necessary in 8 or 4 per cent of the 200 patients and in all cases there were additional factors complicating the pregnancy.

TABLE VIII

Caesarean section

Indications	Number of cases
Contracted pelvis	1
Placenta praevia	1
Elderly primigravida, malpresentation and large foetus	1
Unstable presentation and 2 previous stillbirths	1
Repaired vesicovaginal fistula ...	1
Postmaturity	1
Severe pre-eclampsia at 36th week	1
Aortic stenosis, large child and postmaturity	1
Total	8

The fact that patients with heart disease are, with good antenatal care, well able to stand the strain of labour obviates the necessity of performing a Caesarean section with its attendant maternal and foetal risks. Where a difficult or prolonged labour is expected for reasons (Table VIII) such as contracted pelvis, malpresentation or large foetus, Caesarean section will save the mother the danger of physical exhaustion and the shock of a traumatic vaginal delivery. One patient in the series with severe aortic stenosis and frequent rapidity of pulse had an abdominal delivery, for it is recognized that the effects of this lesion are not always predictable, even with moderate exertion. It was perhaps unnecessary to have performed a Caesarean section in the case of postmaturity, but in the patient concerned there was also an associated anxiety and sleeplessness which could not be allayed; and uterine inertia is so frequently associated with postmaturity that rupture of the membranes is, as a rule, contra-indicated. It may also be said that it is the negation of nice obstetric judgement to allow the patient to embark on labour with the idea that if she reacted badly to it, with restlessness, fatigue and rapidity of pulse, a Caesarean section can be resorted to with impunity.

The Baby

Out of 202 deliveries (2 sets of twins and excluding congenital heart disease) there were 5 stillbirths, or 25 per 1,000 and there were 3 neonatal deaths, a rate of 15 per 1,000 live births. In all but 2 of the stillbirths, or 10 per 1,000, there were complicating features, severe pre-eclampsia in 2 and twin delivery in one. The neonatal deaths can also be corrected to 2 cases, as one was associated with pre-eclamptic toxaemia.

Prematurity was a feature of 56, or 27.7 per cent of the deliveries, which is considerably higher than the 8–10 per cent for all patients. This is not surprising, however, when it is considered that the average length of pregnancy in patients with heart disease is 39 weeks (MacRae, 1948). The degree of cardiac decompensation has no influence on the prematurity rate as seen from Table IX.

Table IX

Prematurity in relation to functional group in cases of spontaneous labour

Group	Number of births	Premature infants	Per cent
1	75	20	26.7
2	105	30	28.5
3	21	6	28.6
4	1	0	0.0
Total	202	56	27.7

The Puerperium

All patients were kept in bed for 14 days and during the 3rd week the ambulatory period was gradually increased, with discharge from hospital at the end of this time. Leg movements under a bed cradle, respiratory and postpartum exercises were given from the start and patients breast fed their babies, unless cardiac decompensation was present. The risk of subacute endocarditis, respiratory tract infection, thrombosis of the deep calf veins is such that a close watch was kept for these complications. One patient in the series developed subacute bacterial endocarditis, which was treated with penicillin for one month. She made a complete recovery and 6 months later was in functional Group 2.

Discussion

A substantial fall in the number of maternal deaths in 1948 has been achieved, despite the fact that 169,514 more women gave birth to children in that year than in 1935; at the same time it is of interest and importance to note the alteration in prominence of the various causes of maternal death during recent years (Table X).

It can be seen from this table that the fall in maternal deaths has been most marked in cases of sepsis, where sulphonamides, antibiotics and careful delivery technique with the use of masks have all played a part. The deaths from haemorrhage and shock have been substantially

Table X

A comparison of the causes of maternal mortality (excluding abortion and ectopic gestation) in England and Wales, modified from the confidential reports submitted to the Ministry of Health on individual maternal deaths in 1935 *and* 1948

Causes	1935		1949		Reduction in deaths	
	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent
Sepsis	575	32.8	34	6.7	541	94.0
Obstetric complications including haemorrhage and shock	399	22.8	182	35.8	217	56.9
Toxaemia of pregnancy	258	14.7	115	22.6	143	55.4
Heart disease	89	5.1	58	11.4	31	34.8
Embolism	153	8.7	56	11.0	97	63.4
Pulmonary infections (including tuberculosis)	103	5.9	15	2.9	88	85.2
Other conditions	171	9.7	49	9.6	122	71.3
Total	1748	99.7	509	100.0	1239	70.9

reduced by means of blood transfusions, but better results await the improvement in the conduct of the third stage of labour. The fall in the frequency of pregnancy toxaemia is due to better antenatal care with early recognition of the slightest departure from a normal course. As regards heart disease, it is not possible to give the number of pregnant women with this complication, but it is obvious from the table that there are still many fatal cases and they have come to occupy a relatively more prominent position as a cause of maternal death. This is further substantiated by Table XI, which shows heart disease as the commonest cause of maternal death in the booked cases of some of our large maternity hospitals.

TABLE XI

Causes of maternal mortality in booked cases in maternity hospitals for the year 1946*

Causes	Number of cases	Per cent
Sepsis	0	0.0
Obstetrical complications including haemorrhage and shock ...	9	29.0
Toxaemia of pregnancy	6	19.3
Heart disease	11	35.5
Embolism	1	3.2
Pulmonary infection (including tuberculosis)	0	0.0
Anaesthesia	2	6.5
Other conditions	2	6.5
Total	31	100.0

*The Simpson Memorial Maternity Pavilion, Edinburgh
Saint Mary's Hospitals, Manchester
The Glasgow Royal Maternity and Women's Hospital
Queen Charlotte's Maternity Hospital, London
The Birmingham Maternity Hospital,
The Princess Mary Maternity Hospital, Newcastle upon Tyne

In patients with heart disease who have had no antenatal care, the mortality rate may remain high, but better results can be expected if the patient reports early in pregnancy and is given strict care and attention. Cardiac decompensation is the great danger but this is largely avoidable; and, by bringing the patient through her pregnancy in relatively good physical strength, the gradual failure of the heart during the first puerperal week, so common in past years, is prevented. Bunim and Appel (1950) have also reported no deaths from congestive heart failure among 202 obstetric patients with rheumatic heart disease, who remained under their care through pregnancy and parturition. It is, at the same time, appreciated that the duration and severity of the rheumatic heart disease affects the expectation of life; and recurrent attacks of acute rheumatism, although rare at this period, may occur as reported by Castleden, Hamilton-Paterson and Rosser (1949).

Termination of the early pregnancy for patients who persist in Groups 3 or 4 after rest and treatment, and for whom the strain of pregnancy is proving too great, further serves to lower the mortality rate. In the present series the therapeutic abortion rate of 3.2 per cent was, nevertheless, moderate and compares well with the rate of 5.3 per cent in a previous series (MacRae, 1948).

The question of terminating pregnancy in a patient with mitral stenosis must, however, receive further consideration.

The great advances in cardiac surgery have brought a new hope to patients with mitral stenosis and congenital heart lesions. One hundred cases of mitral valvotomy were reported by Baker *et al.* (1952) with 13 deaths, of which 7 occurred in the first 20 cases and with good, or excellent results in at least three-quarters of the survivors. Not all patients obtained benefit from the operation because of severe fibrous and other changes in the valve, the nature of which was apparent only at operation.

Logan and Turner (1952) and Brock (1952) have successfully operated during pregnancy on women with mitral stenosis. It would be reasonable, therefore, to consider for valvotomy patients who, despite medical treatment, remain in functional Groups 3 or 4, and for whom continuance of the pregnancy was desirable (and this would include patients for whom therapeutic abortion was contemplated). The operation is thus rarely indicated during pregnancy. It is obvious, none the less, that if there were signs of pulmonary hypertension before pregnancy, it would be of considerable benefit to the patient and would avoid the risk of abortion, if she were sent for operation at that time. Unfortunately, in most instances, advice and treatment are first given at the antenatal clinic.

Some writers have suggested that mass radiography for tuberculosis would be both more economical and beneficial if chest lesions, besides tubercular, were looked for and investigated and in this way reveal at an early stage many unsuspected cardiac lesions. The distant prognosis for patients who have undergone mitral valve surgery has still to be assessed and Jordan and Hellems (1952) contend that the clinical course of these patients generally shows improvement, although a study of the haemodynamics does not indicate any comparable change.

It is common to find at the postnatal clinic that patients, who have had the benefit of antenatal care, are in a fitter condition than before pregnancy.

The question then arises of return to work of patients with heart disease. This has prompted the American Heart Association (1952a) to issue a series of important and far-seeing booklets and leaflets to physicians, patients and employers. The housewife is hereby instructed on the labour-saving methods she could use in order to reduce her physical output and limit the tiredness of long periods on her feet. She is also told of the exact foods which will keep her well and prevent overweight and oedema, and the big range of low sodium and carbohydrate foods available is sufficiently attractive to enable her to continue with such a diet. For the patient who wishes to go out to work, and there is no contra-indication to this in the majority, the booklets give instructions on suitable occupations.

The strict course of treatment for the damaged heart during the antenatal period is exacting alike to patient and doctor, but is justified by the results achieved; and the advances of cardiac surgery and the detailed after care advised by the American Heart Association represent great strides in the future treatment of rheumatic heart disease.

Finally, it is noted that the American Heart Association (1952b), in a nation-wide approach to the family doctor, have issued to them detailed instruction on the prevention and early treatment of rheumatic fever, which is likely to help in the eradication of this disease.

Summary

A series of 228 patients with heart disease is reported without a maternal death.

The corrected stillbirth rate was 9 per 1,000 deliveries and the corrected neonatal death rate 14 per 1,000 live births.

There were 11 abortions, 7 therapeutic (3.2 per cent), and 4 spontaneous (1.8 per cent).

Tables are given to show that heart disease has now become one of the commonest causes of maternal death. The aim of antenatal care was to prevent cardiac decompensation and such treatment is outlined.

Valvotomy may be considered for patients with mitral stenosis who remain in Groups 3 or 4 and where it is hoped to avoid therapeutic abortion.

All patients are referred to a cardiac clinic for further care and the importance of their rehabilitation is emphasized, with special reference to publications of the American Heart Association.

I wish to acknowledge the kindness of the members of the staff of Queen Charlotte's Maternity Hospital who allowed me to look after their cases, from which this series is taken. The cardiac lesions were examined by a number of physicians whom I wish to thank, in particular Dr. Cyril Barnes, who saw patients of the latter half of the series.

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BREAST-FEEDING: FACTORS AFFECTING SUCCESS

A Report of a Trial of the Woolwich Methods in a Group of Primiparae

BY

JOHN BLAIKLEY, F.R.C.S., F.R.C.O.G.

SILAS CLARKE, M.B., B.S.

RONALD MACKEITH, D.M., F.R.C.P.

AND

KATHLEEN M. OGDEN, S.R.N., S.C.M., M.T.D.

From the Departments of Obstetrics, and of Child Health, Guy's Hospital

INTRODUCTION

IN 1946 Waller reported that in a controlled experiment the proportion of primiparae successfully breast-feeding their babies for 6 months had been doubled from 42 per cent in a control group to 83 per cent by certain measures which he described. We decided to see whether his results could be repeated.

For this we had more than one reason. We believed that breast-feeding is convenient for mothers and is a source of genuine satisfaction to many of them; that it is cheaper; that it provides close physical and emotional contact with benefit for both baby and mother. For the baby it is associated with better health; the advantage of breast-feeding babies being, as far as recent large-scale observations in this country go (Douglas, 1950), that they tend to have fewer, milder and later illnesses in their first year of life. We therefore felt that when a mother wants to suckle and feed her own baby, we ought to know what is the best advice to give her. On the other hand, although it was tacitly assumed that women attending our hospital would want to breast-feed, we thought that to lay great emphasis on the benefits of breast-feeding was undesirable, as it would tend to make mothers who did not succeed in breast-feeding feel that they had failed their babies.

The methods in use at the British Hospital for Mothers and Babies, Woolwich

Our interpretation of Dr. Waller's work was that he considers that many of the failures to maintain lactation to the end of the 6th month are due to long continued overdistension of the breasts in the first week of the puerperium; and that to prevent this overfilling he devised measures to be applied (*a*) during pregnancy and (*b*) during the lying-in period.

He states that among the chief causes of this overdistension in the puerperium are poorly developed nipples, incomplete patency of the system of ducts and inelastic skin, the last especially in elderly primiparae. At one time he suggested that the milk-ducts might become blocked by thick colostrum and cellular debris, but more recently the blockage has been ascribed to pressure on the ducts from without by oedema in the breast. The antenatal measures described in his report were designed to ensure that the nipples were mobile and the milk ducts patent. Waller also drew attention to the fact that in some women the yield of milk in the puerperium is far in excess of the infant's appetite and may cause gross overfilling of the ducts, and he advised treatment for this too.

The fully developed nipple usually stands out well from the breast and comes out still further when the areola is pressed between finger and thumb. This is what Waller terms the protractile nipple. A good nipple, being protractile or mobile, is easily drawn away from the breast—the baby can easily get hold of it and suck it well into his mouth. His gums will bite on the skin of the areola over the lacteal reservoirs and the force of his suction will fall on this areolar skin and scarcely at all on the surface of the nipple.

Immature nipples are recognized by their poor general development and by the ducts opening on to a central crater instead of separately on the summit; and by the fact that the nipples are poorly protractile or even retractile, that is to say they go inwards when the areola is pressed between finger and thumb. When the nipple is not mobile, the infant's bite fails to reach the areola and falls on the nipple itself. Hence the infant cannot express the milk from the subareolar sinuses and he may abrade the skin of the nipple. When a nipple is visibly retracted it is usually immobile, but a nipple normal in appearance may also be poorly protractile, so it is important to test for protractility with finger and thumb: inspection is not enough. (It is the second condition which, in our experience, is much commoner.) For either type, glass nipple shields were worn from the 20th week of pregnancy or earlier. The other antenatal precaution Waller described was ensuring that the ducts in the breast were open so that, when milk production began in the puerperium, there would be no interference with the easy flow to the nipple. Cleanliness of the nipples ensured that the openings of the ducts were not blocked by dried secretion; massage of the breast and expression of colostrum daily from the 36th week ensured patency of the ducts within the breast. If difficulty in lactation was expected, massage and expression were started at the 32nd week.

(As it has been suggested that the loss of colostrum by antenatal expression is harmful, it may be noted here that we accept the view that, in the human species, transference of antibodies from mother to child is almost entirely across the placenta and not by way of the milk or colostrum, so that the loss of colostrum is probably unimportant.)

In the lying-in-period Dr. Waller's aim was to prevent overfilling and high tension from milk within the breast, because this leads to resorption of milk, diminution of secretion and, if continued, to involution of secreting tissue. Furthermore, he holds that the tenderness of the overfilled breast is to be avoided because pain inhibits reflex outflow of the milk. The chief measure for prevention of overfilling was the expression of residual milk by the mother after each feed. If the breasts were filling rapidly, partial expression might be done before the feed or feeding made more frequent. If the engorgement became more pronounced and was not controlled by expression, and especially if it was developing rapidly, oestrogens were given to diminish the production of milk temporarily. (It is perhaps not quite clear from Dr. Waller's paper of 1946 that he endeavoured to control engorgement by expression and by giving stilboestrol *before* the engorgement became pronounced.) Engorgement commonly produces oedema not only of the tissues but also of the skin of the areola and nipple. This impairs the protractility of the nipple, which can no longer be sucked well into the infant's mouth and his sucking and biting will fall on the nipple itself. Hence, if sucking is allowed when the breast is engorged and the skin oedematous, then first an abrasion of the skin and then, when this becomes infected, a painful cracked nipple are likely to result. If engorgement occurred, besides the use of massage and oestrogens, suckling was therefore omitted by Waller in order to diminish the liability to sore nipples and infections of the breast.

Outline of work reported here

Our plan was to study some 200 primiparous mothers, half to be controls, and half to practise the Woolwich methods. The mothers in both groups had the usual antenatal advice and care. This included general advice on breast-feeding, advice on suitable brassieres, attention to the nipples and treatment of them with glass shields when necessary. Glass shields were used as we felt they were more effective than plastic ones. The mothers on the Woolwich regime were in addition taught, during the antenatal period, to massage the breasts and express colostrum daily for the last 4 to 8 weeks, and in the puerperium they received special attention designed to reduce the incidence of engorgement. All primigravidae attending the antenatal clinic were seen by one of us (K.M.O.). Of these, all who (1) lived within 3 miles of the hospital and (2) were to be delivered in the ward were the subject material of our main experiment, and were

allotted alternately to the control group and to the group that had the special Woolwich measures.

As it was necessary to observe subjects for at least 4 months before delivery and for 6 months after, the experiment extended over 24 months. The wastage of cases taken under observation was not high. Of 117 cases taken on as controls, 1 had an abortion and 116 were observed to the end of their puerperium; of these 3 were eventually untraced, leaving 113 observed throughout the 6 months after delivery. Of the 117 women treated by the Woolwich methods, 1 had an abortion and 5 lost their babies shortly after birth, so that 111 were observed to the end of their puerperium. Two of these were untraced, leaving 109 who were followed to the end of the 6 months after delivery.

The primigravidae who were to be delivered in their homes "on the district" also all had antenatal supervision by K.M.O., and alternate women were taught manual expression of colostrum from the 36th week (or 32nd in some cases). These were not supervised by us in their puerperium but by district midwives. They were later followed up and the success of breast-feeding recorded. Our observations are fewer in number, but, as is noted below, they point to a conclusion.

The ideas were discussed by the whole team, but the details were planned and supervised chiefly by S.C. and K.M.O. The work took the whole time of one fully trained midwife (K.M.O.). At any one time during the 24 months she had under her immediate supervision 170 to 190 women in the antenatal clinics; and 4 to 8 women in the wards. In addition there was planning, especially at the outset, and follow-up work which increased in the later months. It might be argued that it was extravagant to use the whole time of a trained nurse, but we wanted a clear answer to our question. If it seemed that breast-feeding was helped by the methods under trial, then we planned to apply them as routine, with the expectation that after a "Lactation Sister" had been working in the Department for 2 or 3 years, the methods would have become known to all the midwives and would thereafter be applied by them.

The Daily Routine of the Lactation Sister

The daily routine of the midwife on this work was a busy one. She attended all antenatal clinics, interviewing *all* the patients at their first or second visit, teaching and advising them, supplying glass shields when necessary and supervising their use; and seeing the "W" patients at the 32nd or 33rd week and thereafter, to teach them massage and expression. Secondly, the sister was present, as far as possible, in the wards at feeding times to inspect breasts before and after feeding, to help with difficult feeding and with massage, and to consider whether stilboestrol was needed. Thirdly, she was responsible for the breast-milk bank, collection, sterilization and storage of the milk; and, fourthly, for the collection and recording of observations. She did not supervise the "W" mothers after they had left the hospital. Both "W" and control groups were told they would receive a questionnaire later. If they did not reply to this, the health visitors and district midwives visited them.

Management of Lactation in the Puerperium

For this experiment, we accepted the hypothesis that excessive increase of tension in the breasts during the lying-in period tends to diminish success in the later months of lactation. To prevent such overfilling we endeavoured to encourage efficient feeding by the infants; we used manual expression after all feeds and otherwise when needed; and where necessary we gave stilboestrol.

The four categories of tension of the breast (Waller, 1946), and the management of each, are set out below, so that our ways of dealing with each of them can be clearly understood.

1. *The Normal.* In these, tension scarcely rises and outflow is easy.

The women in this category need no help from the nursing staff in the expression of milk. There may be only a little milk left after feeds, but, even when the yield is high and there is plenty of residual milk to be removed, outflow is free, and the mothers can express it by themselves.

2. *Overload.* In this condition there is a moderate overfilling and rise of tension, which

is easily controlled by manual expression of the excess of milk.

Here some help may be needed at first from the nursing staff. If the breasts were found to refill a considerable time before the next feed was due, an increase in the frequency of feeds was sometimes used to help to diminish the overfilling. A baby who is over-greedy on 4-hourly feeding may feed better at shorter intervals. However, a baby that has to be wakened often feeds inefficiently, and a better way to deal with the problem of very rapid refilling of the breast is by additional expression between feeds. The argument that more frequent feeds or expression are bad because "the more you take off the more comes in and this encourages rather than relieves overfilling" does not convince. The steps we took were taken to prevent overfilling and, if refilling was rapid, removal of the milk had to be frequent. Even if the output of milk was increased by the massage and expression, the latter did prevent the overfilling which we considered the serious problem.

3. *Engorgement.* This is a greater degree of overfilling, often with recognizable oedema of the skin.

Great vigilance and much help from the nursing staff are called for. Engorgement is reduced by manual removal of milk. The presence of oedema in the tissues of nipple and breast makes the nipple less fully protractile and so the baby's bite may fall on the nipple skin, itself oedematous and liable to damage. If oedema is present in the skin, suckling is withheld until it has subsided, tension being relieved meanwhile by massage only. (Massage alone without digital expression is used because handling of the areola tends to increase the oedema.) When feeding is allowed, it is preceded by removal of some superfluous milk; and after the child has fed it is usually necessary to empty the breast further by hand. Stilboestrol is sometimes needed; its use is discussed below.

4. *Engorgement with Obstruction.* This is the extreme type with greatly swollen breasts, oedematous skin and nipples, and no outflow.

The breasts are raised and firmly supported and no attempt at feeding allowed. Emptying by hand is begun as soon as any outflow can be obtained. When this becomes free and all trace of oedema has disappeared suckling is allowed, excess of milk being still removed before and after feeds. Stilboestrol is always required for such cases.

The use of Stilboestrol as an accessory to Suckling and Expression for Prevention and Treatment of Severe Engorgement of the Breasts.

Our ideas on the use of stilboestrol may be set out in some detail because developing a skill or clinical judgment in using this potent drug is, we think, an important factor in getting good results with this regime. Stilboestrol is to be used when suckling and expression fail to relieve overfilling. It is not a substitute for these two measures but should not be withheld when, for example, the lumpiness in the breast is still unrelieved after feeding followed by expression. Once the milk is running, where no night feed is given, the breasts are commonly full before the first morning feed and this fullness may not be completely relieved until after the second feed of the day. Stilboestrol is more likely to be needed if the baby feeds poorly or if the breast refills with rapidity. Experience teaches its proper use, both when to give it and in what dose. A small dose given early is likely to be more successful than a large one given after severe engorgement has developed, and the smaller earlier dose probably has the advantage that the duration of the effect is briefer. The mother's attendants should endeavour to recognize the cases likely to develop engorgement. On the first day of the puerperium, the doctor or the sister of the lying-in ward should, if this has not already been done at the antenatal clinic, make an examination and assess the likelihood of severe engorgement.

Engorgement may be expected when:

(i) there is already a history of previous severe engorgement;

(ii) the skin on the breast is thick and inelastic.

In such cases special vigilance is required and the mother may be advised to tell the nurse

as soon as she feels any overfilling of the breasts, aching, lumpiness or heaviness.

There are two further warnings that may be noted;

(iii) the baby feeds poorly; and

(iv) the breasts fill or refill after the feeds with rapidity.

Sometimes increasing the frequency of feeds or extra expression between feeds may help to diminish the overfilling. *Stilboestrol is indicated when suckling followed by expression does not obviously relieve the increased tension in the breasts.*

When it has been discovered that tension persists after a feed, stilboestrol is given orally. A small dose is 5 mg. This will often be sufficient. If a more severe overfilling has occurred, larger doses of stilboestrol are needed, e.g., 10–15 mg. for Waller's type 3 of tension of the breast, or 20–25 mg. or more for Waller's type 4 of tension of the breast. At these stages small doses are useless.

(v) *The situation must always be reviewed at the next feed or not longer than 4 hours after the stilboestrol has been given.* If the tension has been lowered and milk can now be withdrawn, it is wiser to give no further dose, for stilboestrol has an effect lasting beyond the 4-hour period. If the tension in the breast is unrelieved, a further dose is given, 5, 10, 15 mg. or more, depending on whether there is any suggestion of improvement or of exacerbation. The situation is reviewed regularly and stilboestrol repeated 4-hourly until improvement occurs. If an 8-hour interval between feeds at night has already been established, waking the mother and child after 4 hours is wise when engorgement is present or threatens.

After stilboestrol has been given in the puerperium, there is always a decrease in the amount of milk, which may necessitate complementary feeding for the time being. Provided that the breast is emptied every 4 hours by suckling or manual expression the secretion of milk will be back to normal in a day or so, or at the latest in a week.

We gave stilboestrol to 38 out of our 117 women treated by the Woolwich methods.

Stilboestrol is a powerful drug but early use may obviate heavy dosage. Where the doctor believes that there is danger of engorgement developing suddenly in his absence, he may think it justifiable to prescribe the drug, leaving the decision as to the necessity, the moment of administration, and the amount of the first dose, to the midwife who is in constant attendance on the mother. Delay in getting permission to give the drug may prevent success in its use. The doctor in charge must know the indications for stilboestrol and the suitable doses. He has to teach whoever is in immediate attendance on the mother what to look for and when and how much to give. The person on the spot may be a doctor, if he is constantly available, or a midwife. It has been found profitable, both at Woolwich and initially at Guy's, for one sister to devote especial attention to lactation. This sister, with her experience and developed judgment, is to be consulted before any urgently required stilboestrol is given in the absence of a doctor. Once one is satisfied that the midwife's experience and judgment are good, then she should be given scope to use them.

Results

Breast-feeding in cases delivered in hospital (Table Ia and Ib)

The results obtained for the mothers delivered in hospital are summarized in Table Ia. The term " fully breast-fed " indicates that the only source of liquid milk was the infant's mother's breast. The children were usually having solid foods from the 4th or 5th months and a little cow's milk might be given in these.

Among the cases delivered in hospital (Table I) the difference between the two series in the proportion fully breast-fed at the end of the lying-in period is not statistically significant.*

In this group, successful breast-feeding for 6 months was achieved by 26 per cent of the controls and 51 per cent of the " W " mothers. This difference is highly significant.

* Conventional levels of significance are used in this paper. If the probability that an observed difference could arise by chance is less than 1 in 20, it is termed significant; if less than 1 in 100, highly significant.

The rate of falling off of breast-feeding is shown in Table Ib and the graph. There is some suggestion that the difference between the "W" and control groups widens after the 8th week, which might be because those who failed were unable to meet increasing demands after the 2nd month but the point is not established.

Neonatal Deaths

It will be noted in Table II that there were 5 infant deaths among the children born to the mothers treated by Woolwich methods, and none among the control mothers' infants. Of these 5 infants, further details must be given.

The first was a boy, born 5 days overdue, weighing 6 pounds 11 ounces. He had blue asphyxia at birth, improved a little, but never fed and died on the 3rd day. He had a cor triloculare and a small intracranial haemorrhage.

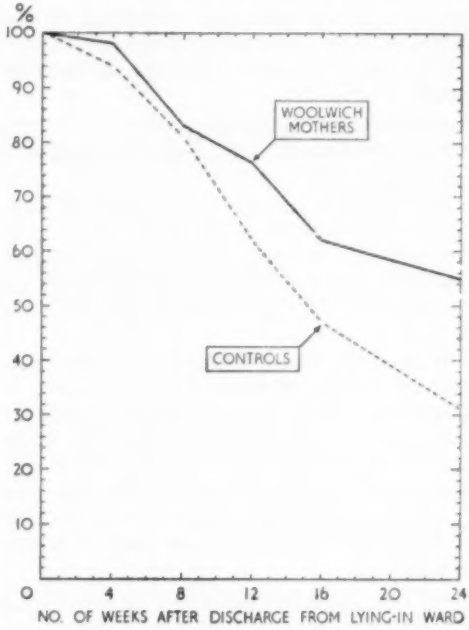
The second was a boy born 10 days early, weighing 7 pounds 1 ounce. After delay in the second stage he was delivered with forceps. There was excessive moulding and his condition from birth was poor, with recurring fits till he died on the 3rd day. There was much subarachnoid haemorrhage with two tentorial tears.

The third was a boy, born at term weighing 8 pounds 6 ounces. He progressively lost weight and at 12 days old began to vomit and died at 15 days old. At necropsy urethral obstruction with distension of bladder and lower ureters was found.

The fourth was a girl, stillborn at term, weighing 6 pounds 12 ounces, with congenital abnormalities, talipes, spina bifida and mild hydrocephaly.

The fifth was a foetus weighing 2 pounds 9 ounces, delivered at the 27th week to a mother with chronic rheumatic carditis. It survived to the 4th day.

The necropsy findings are reassuring. In the first 4 cases it is impossible to relate these deaths to the special antenatal regime adopted for this group as contrasted with the control group. In the 5th case the infant was delivered at 27 weeks, before the special Woolwich measures were begun.



Percentage of mothers fully breast-feeding (expressed as percentages of number of mothers breast-feeding at discharge from ward)

Incidence of Complications (Table II)

A summary of the complications seen is given in Table II, in which the terms employed are defined as follows:

"*Engorged breast third and fourth degree*", the third and fourth categories of tension described by Waller (1946) and mentioned above.

Flushed breast. This expression implied local redness and lumpiness of the breast unaccompanied by general disturbances such as anorexia of pyrexia.

Mastitis. Local inflammation of the breast with general disturbance of health. (This condition called for treatment with, e.g., penicillin, and, recognized early, is usually controllable.)

Breast abscess. Localized formation of pus in the breast requiring incision and drainage.

As regards complications, the difference between the two groups during the lying-in period is highly significant whether one takes the third and fourth degree engorgement only or all

TABLE Ia

Cases Delivered in Hospital
(percentages, in brackets, are expressed in nearest whole number)

	Control group	Group on Woolwich methods
Number of pregnancies observed	117	117
Cases lost:		
Abortions	1	1
Deaths	0	5
Number of mothers observed at end of lying-in period	116	111
Method of feeding infants at end of lying-in period:		
Fully breast-fed	97 (84)	102 (93)
Breast and bottle	15 (13)	8 (7)
Wholly bottle-fed	4 (4)	1 (1)
Cases untraced at end of 6 months	3	2
Number of mothers observed for 6 months	113	109
Method of feeding at end of 6 months:		
Fully breast-fed	30 (26)	56 (51)
Possibly breast-fed	2 (2)	3 (3)
Wholly or partly bottle-fed	81 (72)	50 (46)

TABLE Ib

Rate of Falling-off of Breast-feeding: Cases Delivered in Hospital

	Number of mothers observed to end of lying-in period	*Numbers of Mothers fully Breast-feeding* The numbers in brackets are the percentages of mothers breast-feeding expressed as percentage of numbers of mothers fully breast-feeding at discharge from lying-in ward					
		On discharge from lying-in ward	at 4 weeks	at 8 weeks	at 12 weeks	at 16 weeks	at 24 weeks
Group on Woolwich methods	111	102 (100)	100 (98.0)	85 (83.3)	78 (76.5)	65 (63.7)	56* (54.9)
Control group	116	97 (100)	91 (93.8)	79 (81.4)	60 (61.9)	46 (47.4)	30* (30.9)

*Mothers not traced and mothers of whose breast-feeding there was any doubt are counted as *not* fully breast-feeding

complications. The difference between the incidence of complications in the two series between the 2nd and 27th weeks after delivery is not significant, though, in view of the other result, the difference might perhaps be given some weight as supporting evidence.

It may be noted that the incidence of recorded complications is five and a half times higher in the lying-in period than in the rest of the 6 months; which is what one would expect.

Results of wearing Glass Shields for poor Nipples (Tables III and IV)

Of the 234 patients observed, 52 were considered to need treatment because, when examined at the antenatal clinic, the nipples were

TABLE II

Complications: Cases Delivered in Hospital

	Control group	Group on Waller's Methods
A. Complications of foetus or babies:		
Number of pregnancies observed	117	117
Abortions	1	1
Infant deaths	0	5
B. Complications of mothers:		
(1) In lying-in period:		
Number of mothers observed in lying-in period	116	111
Engorged breast, third degree	40	16
Engorged breast, fourth degree	3	1
Cracked nipples	9	4
Flushed breast	1	1
Mastitis	2	0
(2) Between 2nd and 27th week after delivery:		
Number of mothers observed for 6 months ...	113	109
Flushed breast	4	1
Mastitis	2	1
Breast abscess	4	2
Total infections of breast	10	4

TABLE III

Results of Treating Retracted and Immobile Nipples with Glass Shields

	Complete correction	Good improvement	Slight improvement	No benefit
Moderately poor protraction, 36 cases	17	18	1	–
Severe cases, including 2 of visibly retracted nipples. 16 cases	2	12	2	–

TABLE IV

Treatment of Poor Nipples by Glass Shields: Comparison of forecast and actual results

	Complete correction	Good improvement	Slight improvement	No benefit
Forecast favourable, 18 cases	14	4	–	–
Forecast doubtful, 20 cases	3	16	1	–
Forecast unfavourable, 14 cases	3	9	2	–

poorly protractile. Two had obviously retracted nipples on inspection; in the remaining 50 women the immobility of the nipples was only appreciated when they were tested by pressing behind the nipple with finger and thumb. This simple test is important. It should be made early in the woman's pregnancy.

Treatment in almost every case was started by the 20th week in pregnancy. When it was begun, a forecast was made whether there would be an improvement or not. Table III shows the satisfactory results of wearing glass shields. Of 16 severe cases, 14 showed good improvement; and of 36 moderately poor protractile cases, 35 had good improvement. Table IV shows that the actual results of treatment were better than expected.

As regards success in lactation, of the 36 moderately bad cases, 7 fully breast-fed their babies and 8 for 16 weeks, and of the 16 severe ones 7 fully breast-fed and one for 16 weeks.

Late Results in Women given Stilboestrol (Table V)

Table V summarizes the use of stilboestrol. It is evident that used as described here, large doses of stilboestrol do not permanently inhibit lactation. A noteworthy point is that all the larger doses of stilboestrol were given to women in the first half of the series, showing that the technique controlling engorgement improved with experience. To this, improved control by mechanical means and also the earlier use of stilboestrol probably contributed.

TABLE V
Summary of Use of Stilboestrol

Largest dose given	... 110 mg.
Smallest dose given	... 5 mg.
Average dose given	... 33 mg.

Analysis:

100–110mg. given to 4 mothers
Results:
- 2 breast-fed infants to 24 weeks.
- 1 breast-fed infant fully to 8 weeks and partly to 24 weeks.
- 1 failed (complicated by very immature nipples)

50–90 mg. given to 5 mothers
Results:
- 4 breast-fed infants to 24+ weeks. (one fed twins)
- 1 breast-fed infant to 13 weeks.

5–15 mg. given to 29 mothers
Results:
- 13 breast-fed infants to 24+ weeks.
- 3 breast-fed infants to 20 weeks.
- 4 breast-fed infants to 18 weeks.
- 2 breast-fed infants to 16 weeks.
- 3 breast-fed infants to 14 weeks.
- 3 breast-fed infants to 12 weeks.
- 1 failed to breast-feed (no milk).

Breast-feeding in Cases Delivered on District (Table VI)

Among the mothers delivered on district there is no significant difference as regards the numbers breast-feeding at the end of 6 months between the control series and the ones who had Woolwich methods antenatally, nor between these and the control group of the women delivered in hospital.

Dr. Fraser Roberts has drawn our attention to a discrepancy between the hospital and district cases in that, while the numbers wholly bottle-fed at the end of the lying-in period are comparable (1 of 66, and 5 of 227), the numbers having both breast and bottle are very different: none of the 66 district cases as compared with 23 of the 227 delivered in hospital, a difference which is highly significant.

The explanation is complex. It is not merely because milk for complementary feeding is more readily available in hospital. In hospital a baby is often handled by a larger number of different people, some of them relatively inexperienced persons in training. Furthermore, the baby may be disturbed by going from a nursery to a ward at a different temperature. If a baby is a slow or difficult feeder the mother will receive help and advice from nurses, and as there are day and night nurses the advice may vary from time to time. There are more difficult deliveries—forceps and otherwise—among the hospital cases and so it is likely that among the babies delivered in hospital there will be more who feed slowly or with difficulty. For all these reasons these infants may have an excessive loss of weight and be given complementary feeds. In addition, the babies in hospital were fed at regular intervals by the clock. If there was any difference in the district babies they would be on a less rigid schedule; and as it has been shown (Illingworth *et al.*, 1952) that babies fed "on demand" gain

TABLE VI

Success or Failure in Breast-feeding: Cases Delivered on District

(percentages, in brackets, are expressed in nearest whole number)

	Control group	Group on Woolwich methods
Number of pregnancies observed	66	64
Method of feeding at end of lying-in period:		
Fully breast-fed	65	64
Wholly bottle-fed	1	
Cases untraced during 6 months	1	5
Number of mothers observed for 6 months ...	65	59
Method of feeding at end of 6 months:		
Fully breast-fed for 6 months	20 (31)	13 (22)
Wholly or partly bottle-fed	45 (69)	46 (78)

weight faster, there might well have been less reason among the district babies for giving complementary feeds. (On the other hand the same paper showed that where the baby was on "demand" feeding, the chance of successful breast-feeding was greater.) Test weighing is easier in hospital, and this probably reveals some babies who are quiet but grossly underfed. Such babies may carry on unrecognized for 2 weeks and so may be recorded as having no bottle feeds by the end of the lying-in period. By the 3rd week the underfeeding becomes evident and they are put on bottle-feeding.

It may be observed that while there is a significant difference in the incidence of complementary feeding between hospital and district babies, the difference between its incidence in control mothers (13 per cent), and Woolwich mothers (7 per cent) is not significant.

COMMENT

Our observations on primiparae delivered in hospital showed that, among the mothers on the Woolwich regime, 51 per cent successfully fed their babies for 6 months, compared with 26 per cent of the control mothers. This difference is highly significant and we conclude that the Woolwich regime was responsible for the greater success.

Waller (1946) reported a rise from 42 per cent in his controls to 83 per cent, and it may be agreed that our control group level of 26 per cent is unusually low and hence that a rise to 51 per cent could be achieved with ease. We admit that 26 per cent is a lower figure than we expected, but the general level in the country is about 20 per cent breast-fed for 6 months, and to achieve a figure of 51 per cent is a satisfactory increase.

Among the primiparae delivered on district there was no difference, as regards success in breast-feeding for 6 months, between the control and Woolwich groups, both having the same level as the control group among the mothers delivered in hospital. This points to the conclusion that the supervision in the lying-in period is what counted. If this is so, then the antenatal massage and expression may be considered simply as preparation for the use of these methods for removing surplus milk after feeds in the puerperium. It is "learning expression for use at the lying-in" rather than expression "to ensure patency of the milk ducts".

We concluded that the good results in the "W" women delivered in the hospital depended on the care they received in the lying-in period and probably on the skill, both at supervising expression in engorgement and in the use of stilboestrol, which K.M.O. acquired from her training and experience. It remains uncertain whether the same improvement would be obtained by applying these methods to all

the women attending a maternity department. It might be that the staff would not have the time or the special knowledge (e.g., of the use of stilboestrol). We consider that if these methods are to be introduced, it should be done gradually, giving one midwife in a department special responsibility and special opportunity of gaining experience. The duties of such a "lactation sister" are responsible and include also work in the antenatal clinic and the management of the hospital breast-milk bank.

Since the results of treatment of retracted and immobile nipples were observed to be good, we came to recommend that even the mildest deformity of the nipple should be treated early by the use of glass shields. It also became evident that it is justifiable to promise benefit from this treatment.

The results of our whole series afford strong support to Waller's theory that his measures for prevention of puerperal engorgement increase the chances of successful breast-feeding. How they work, is not established certainly. A contributory factor may be the confidence which this system gives to the mother. Before leaving hospital she has been shown how to deal with lumpiness of the breasts or soreness of the nipples. Knowing how to handle her breasts and cope with excessive milk gives her confidence in her ability not only to feed but also to deal with such minor setbacks when she has left the lying-in ward. It is not a kindness to pretend that breast-feeding is always easy.

Because it has been suggested that handling the breasts is likely to cause increased infections, it is also worth drawing attention to the fact that the incidence of complications was highly significantly less among the mothers on the Woolwich regime; to be able to prevent so much painful suffering is a considerable advance.

A valuable product was breast-milk. Throughout our experiment, although at any moment there were only 4 to 8 mothers in the lying-in ward doing expression after feeding, a supply of breast-milk was available for infants in the maternity wards and for sick babies in the hospital.

The relative cost of breast-feeding and artificial feeding is not easily calculated with exactness. The cost of dried milk powder varies. National dried milk is a subsidized product. The proprietary milks in the clinic pack are twice the price of N.D.M. and, bought at the chemist, they are four times the price. The extra cost of bottle-feeding from the end of the 2nd month is of the order of £10. In our experiment of the mothers practising the Woolwich method, 25 per cent more breast-fed their babies for 6 months. If the results are applicable on a larger scale, then in a unit dealing with 800 deliveries a year, there would be 200 extra successful lactations. This would mean a saving of £2,000—not to the hospital, but to the national exchequer. It is possible that the appointment of a lactation sister represents a valuable economy. Professor Charles McNeil (1942), 10 years ago, said that 5,500,000 gallons of mother's milk were wasted yearly by unnecessary weaning of infants.

SUMMARY

(1) The methods which Waller (1946) from the British Hospital for Mothers and Babies at Woolwich reported as doubling the incidence of success in breast-feeding babies for 6 months have been applied to 117 mothers and 117 controls in a group of primiparae delivered in hospital.

The experiment is described with a detailed report of our method of using stilboestrol.

(2) Twenty-six per cent of the controls and 51 per cent of the mothers on Woolwich methods successfully breast-fed their infants for 6 months (Table I).

(3) Severe engorgement and cracked nipples in the lying-in period were much less common among the mothers on the Woolwich regime (Table II).

(4) Good improvement can be promised to nearly all cases of retracted nipples if they wear glass shields for the last 3 months of the pregnancy (Tables III and IV).

(5) A group of primiparae on a similar antenatal regime but delivered at home showed no greater success in breast-feeding than did the control group (Table VI).

(6) We conclude that the important factor in promoting successful breast-feeding for 6 months

is close supervision and care during the lying-in period, and that probably the important item in this care is the prevention of long continued overfilling of the breasts by regular removal of surplus milk after feeds and by judicious use of stilboestrol.

(7) We conclude that massage and expression should be learnt antenatally so that it can be used in the lying-in period.

(8) An outline with some practical details of the Woolwich regime is given in an appendix to this paper. It was found valuable when the regime was applied to all mothers.

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APPENDIX

Breast-feeding: Woolwich Regime as Used at Guy's Hospital During This Investigation

In Antenatal Clinic

(1) At first visit to lactation department:

(*a*) History of previous lactations.

(*b*) Scrupulous examination of breasts, noticing and recording: (i) size and shape; (ii) skin elasticity; (iii) old scars; (iv) nipples (size, shape, number of external openings, apply test for protraction).

(*c*) Advice *re*:

(1) Breast-feeding: (i) emphasis on convenience and enjoyment rather than on it being a duty or necessity, and (ii) giving mothers a chance to ask questions.

(2) Breast hygiene, no scrubbing or application of spirit to nipples.

(3) Brassiere.

(*d*) Fit shells where necessary in all severe cases of retraction or bad protraction. Shells should be worn by 16th to 20th week.

At subsequent attendances:

(2) Follow up all cases wearing shells, seeing at every clinic visit.

(3) Teach all cases massage of breasts with expression of colostrum: (i) from 32nd week where lactation difficulties are anticipated; (ii) from 36th week to all normal cases, telling mother to practise daily for 5 to 10 minutes.

(4) At every further attendance watch patients doing their massage and expression until proficiency is attained. (At the present moment this antenatal massage and expression is not being taught, in order to find out whether it is necessary.)

(5) Inform ward sisters in advance of all cases where difficulties may arise so that the ward sisters may be extra vigilant.

In Lying-in Wards

Before feeds

(1) Inspection of breasts and nipples.

(2) Educate mother in simple anatomy of breasts and show her the most comfortable way in which to hold her child for feeding.

(3) When lactation is established teach mothers to get milk flowing before putting child to breast.

(4) No child to go to breast if nipples feel sore, look sore, are oedematous.

During feeds

Help any pair who need assistance, aiming for the mother to learn to know her baby and its feeding so she won't feel lost when she gets home.

After feeds

(1) Thorough breast and nipple inspection.

(2) Mothers to empty their breasts manually after each feed, until such time as sister considers the child is adequately emptying them and/or that there is no need for extra stimulation (see further notes below).

(3) Sister to give special supervision to mothers with engorgement, deciding: (i) whether to give stilboestrol and how much of it (see further notes below); (ii) whether, while continuing massage, to omit expression, because skin is oedematous.

(4) Supervising application of binders.

(5) Supervision of milk collection and sterilization.

Guides to how long manual expression after feeds should be continued.

Expression after feeds is done for two reasons.

(*a*) To prevent overfilling in those women with more milk than the infant takes.

(*b*) To encourage milk production in women with poor supply.

The aim is for the mother to learn when she needs to express, so that she does it willingly and so that when she has gone home she will know how to do it, if for some reason such as a mild illness, the child does not fully empty the breast at any feed. The breast must be emptied at or after each feed so that

there is no raised tension when feed is completed. The mother is to be taught to appreciate this.

(1) Expressing after feeds is always continued until the end of the 7th day.

(2) If surplus is then only half-an-ounce or less, expression is discontinued.

(3) If milk supply is poor, expression of ALL remaining milk is continued until supply is sufficient to keep the infant "happy and growing."

(4) If mother is a large producer, expression of milk —or nearly all, the last half-ounce does not matter— must be continued. The child will catch up or the excess production diminish in 3 or 4 weeks. The mother must appreciate the importance of continuing expression, so she can be trusted to carry on at home.

(5) If excess is large, judicious use of small doses of stilboestrol, 3 mg. daily for 3 days, may be tried if mother is under supervision of a knowledgeable person.

Guides to the giving of stilboestrol for engorgement

(1) If tension has only recently begun to rise, give small doses, i.e. 5 mg., and review situation 4 hours later—when probably no further dose is needed.

(2) If engorgement has already developed a large initial dose is essential—15 to 25 mg. according to severity and rapidity with which it has developed; thereafter review 4-hourly. If tension has lessened and milk flows, follow up with a smaller dose, remembering that the drug continues to act for a period of 8 hours.

If there has been no relief repeat the large dose.

NOTE: Provided the breast is stimulated by manual expression or the baby suckling at regular intervals, within 3 or 4 days the temporary suppression caused by stilboestrol will have ceased and the breasts will be secreting to their full capacity.

THE FAILURE OF THERAPY IN THE MANAGEMENT OF INFERTILITY

BY

TOM BARNS, M.A., B.M., M.R.C.O.G.
Research Fellow, Department of Obstetrics and Gynaecology
Newcastle General Hospital

H. CAMPBELL, B.A., F.S.S.
Statistician, Department of Industrial Health, Durham University

AND

LINTON SNAITH, M.D., M.S., F.R.C.S., F.R.C.O.G.
Senior Obstetrician and Gynaecologist, Newcastle General Hospital

INTRODUCTION

SEVENTY years ago Matthews Duncan wrote: "A reputation for curing sterility is spoken of as if it were founded on substantial claims. As in other departments of therapeutics there has been a great failure in logic: the *post hoc* and the *propter hoc* have been confused, a coincidence has been regarded as a consequence, and the credulity of patients and doctors alike has been the basis for useless and injurious practice."

Today the position is unchanged. Belief in the effectiveness of present-day methods of treatment is widespread and uncritical. Couples in whom the first conception is delayed, sometimes only by a few months, are referred in increasing numbers to centres specializing in the investigation and treatment of this condition, since it is generally believed that a cure can thereby be obtained.

Many gaps exist in our knowledge of current reproductive patterns; not least of these is our ignorance of the natural rate of conception among women at various ages, and after varying durations of infertility. It is not difficult to obtain information of this nature regarding women who have already succeeded in achieving pregnancy. Table I indicates the average time of exposure before first conception, according to the age of the woman, in 1,150 women attending the antenatal department at the Newcastle General Hospital during the year 1952.

Evidence of the probability of unaided conception in the infertile woman, according to the age and duration of infertility, is less readily accessible. Since demographic data take no account of voluntary sterility practised in the individual case, only limited information concerning this problem can be gained from these sources. The only access we have to patients in whom these details are available is through the medium of the Infertility Clinic, and here the findings are vitiated as soon as investigation and treatment is begun, because the majority of the diagnostic procedures in common use are supposed to have a simultaneous therapeutic effect.

Bender (1952) recently analyzed a series of 324 pregnancies, occurring among 700 patients in whom he assumed therapeutic success for all those who conceived within a period of up to 6 months after the cessation of treatment. This author considered that no more than 50 per cent of these pregnancies could be regarded as attributable to treatment, and this report necessarily casts doubt upon many of the results reported by other workers in the field of infertility.

TABLE I
Time taken to Conceive according to the Age of the Patient

Patient's age	Cases	Average exposure
20 years or under	196	2.9 months
21 to 24	442	7.3 months
25 to 29	341	15.0 months
30 to 34	127	27.1 months
35 and over	44	42.4 months
Total	1150	

The Clinical Material in the Present Series

The records of 2,800 patients who attended the Infertility Clinic at the Newcastle General Hospital between April 1943 and April 1952 have been reviewed. Those records containing insufficient data, or relating to patients with secondary or relative infertility or with habitual abortion, were excluded from the series. After excluding a further 32 patients who were already pregnant when they first attended the clinic, 1,208 records remained all of which referred to patients who were suffering from primary infertility. During the course of this review it proved possible to define a group, sufficiently large for purposes of statistical comparison, which was composed of patients who had either received no investigation or treatment of any kind, or in whom the procedures undertaken had been limited to bimanual examination and the performance of post-coital test. For the purposes of this study it has been assumed that this test has no therapeutic value.

At this Infertility Clinic, anamnesis and general physical examination occupy the patient's first visit to the clinic. An appointment for the next attendance is usually given at the time of the next mid-cycle, when a post-coital test is performed. If an unsatisfactory result is obtained from this test, arrangements are then made to interview and investigate the husband. The general policy is to obtain satisfactory evidence of fertility in the male partner before proceeding with further special investigations of the wife.

Analysis of the number of attendances of each patient showed that 19 per cent failed to return to the clinic after their first visit, and a further 13 per cent stayed away following their second visit. One of the reasons for this failure to return was the husband's unwillingness to participate in the investigation, in others a major fault discovered on seminological examination resulted in further treatment being abandoned. Records of certain other cases showed that subsequent attendances had been spent in the repetition of seminal assays, without any treatment of the wife having commenced.

It thus proved possible to select from the main series 501 patients who had received no treatment of any kind, and no investigation other than bimanual examination or post-coital test. A bias against this untreated group was introduced because it included 65 cases in which the male partner was found to be azoöspermic in comparison with the incidence of only 20 cases of azoöspermia in the group which did receive treatment. This should tend to decrease the number of pregnancies occurring in the untreated group.

Except in those patients who had undergone hysterectomy, who were suffering from genital tuberculosis, who were already known to have become pregnant, and certain other cases overlooked by clerical errors, a letter was sent out to all patients in this series who had ceased to attend the clinic asking them to report whether or not they had yet become pregnant. Eight hundred and two questionnaires were sent, 531 patients replied (66 per cent). The proportion of replies received from both groups was comparable; 69 per cent from the treated group, and 62 per cent from the untreated group.

Twenty-five per cent of the patients were aged between 21 and 25 years; 39 per cent between 26 and 30; 25 per cent between 31 and 35; 10 per cent were 36 years of age or more. Table II illustrates the duration of infertility at the time of the first attendance which ranged from 1 to 13 years. In 12 per cent of the patients it was 1 year's duration, in 30 per cent of 2 years, in 31 per cent 3 to 4 years, and in 27 per cent of 5 or more years duration. Seven hundred and seven patients received some form of treatment, or underwent an investigation of possible therapeutic value. Tubal insufflation was performed in 570 cases (81 per cent); hysterosalpingogram in 98 (14 per cent); endometrial biopsy in 396 (56.5 per cent); and hormone therapy in 247

TABLE II
Duration of Infertility before Attending Clinic

Duration of infertility	Cases	Percentage
1 year	145	12
2 years	351	30
3 years	198	16
4 years	180	15
5 years and over	334	27
Total	1208	100

(35 per cent). A variety of other forms of treatment, including manual re-position of the uterus, the use of vaginal dilators, physiotherapy and psychotherapy, cauterization of the cervix, plastic enlargement of the introitus, Gilliam's operation, salpingostomy, myomectomy, and anti-tuberculous chemotherapy were given in 186 patients. There were 501 patients, however, who received no treatment of any kind.

Seven per cent of the husbands were found to be azoöspermic, and in 27 couples (2.3 per cent) the marriage had not been consummated. Gross pelvic pathology was present in 26 patients (2.2 per cent), and pelvic tuberculosis was diagnosed in 46 other cases, an overall incidence of 3.8 per cent, comprising 11.6 per cent of all patients on whom endometrial biopsy had been performed.

The Incidence of Pregnancy

There was an overall incidence of 255 known pregnancies (21 per cent), among the complete series. One hundred and sixty-two of these patients (63 per cent) became pregnant while attending or within 6 months after their last attendance at the clinic. According to the standards used by Bender (1952), referred to above, these pregnancies might appear to be attributable to treatment.

Study of the individual case records, however, showed that some of these patients were not actually receiving treatment at the time they conceived but were merely attending for periodical review. When the incidence of pregnancy was separately studied among those patients who had received treatment and those who had not, it was found that in the untreated group 92 pregnancies were recorded (18.4 per cent) whereas in the treated group 163 pregnancies took place (23 per cent). There was thus little difference in the incidence of pregnancy between the two groups ($\chi^2 = 3.5$; $P > .05$).

The incidence of pregnancy, according to the type of treatment adopted, if any, is indicated in Table III. In each case a comparison may be made with (1) incidence of pregnancy in patients not receiving that particular form of therapy, and (2) the incidence of pregnancy among the group not treated at all (18.4 per cent). It is evident that, except in the treatment of patients who are childless on account of failure to consummate marriage, there was no significant variation in the number of pregnancies following any particular form of therapy. The incidence of pregnancy following hysterogram would appear to be an exception to this statement; the lower incidence, however, is explicable since the cases subjected to hysterogram were selected from women suspected of having tubal occlusion following one or more negative insufflation tests. It is our practice never to subject a patient to hysterogram unless previous insufflation has proved negative, or there exists strong suspicion of tubal disease as a result of previous inflammatory changes in the pelvis.

TABLE III

Type of treatment	Total cases		Percentage becoming pregnant	
	Treated	Untreated	Treated	Untreated
Treatment for failure to consummate marriage	27	1181	44	21
Insufflation	570	638	21.8	20.6
Hysterogram	98	1110	15	21.6
Biopsy	396	812	26	19
Hormones	247	961	22	21
Other forms of treatment	186	1022	23	21
All cases	707	501	23	18.4

Selection of a Homogeneous Group

Since, in the whole group of 1,208 patients, there were no apparent differences in the rate of achieving pregnancy after treatment, it was possible that this lack of difference may have been due to our failure to follow up certain patients as effectively as others. Some had been

followed for 9 years, and others for only one visit. It was, therefore, decided to isolate a group of patients displaying primary infertility who had been followed for 2 years, and only to include those pregnancies which commenced within this two-year period, reckoned from first attendance at the clinic.

This selection reduced the numbers considerably; 390 who had first attended between 1st April, 1950, and 1st April, 1952, were automatically excluded, and it was found that, of the 818 who attended before 1st April, 1950, 251 (31 per cent) had ceased to attend within 2 years, and had failed to reply to the questionnaire. Although this is a large percentage to exclude, it is not possible to speculate on the effect this exclusion might have; it is known, however, that 119 of them (47 per cent) had received treatment, compared with 69 per cent in the remainder.

This left 567 cases, all of whom had been followed for at least 2 years from their first attendance. Some of these had received treatment, and some had not, for the same reasons as those given above. The total number of pregnancies by the end of the 2-year period was 156 (28 per cent). The proportion of pregnancies in the untreated group was 30 per cent, which was slightly higher than in the untreated group, 26 per cent, but the difference is not statistically significant ($\chi^2 = 0.9$; $P > .05$) (see Table IV).

It may be noted that a further 44 of these women became pregnant at some time after the 2-years follow-up period.

Treatment

As in the case of the larger unselected group of 1,208 cases, when individual treatments are considered in detail, there is no evidence in favour of any particular treatment, as is shown in Table V.

In the majority of cases the women who received no treatment were apparently more successful than those who were treated. This difference is statistically significant in the case of hysterosalpingogram, and also in the group dealt with by insufflation. This difference is probably due to the fact that cases submitted to insufflation, and especially those referred for hysterogram, were cases in which there was suspicion of some pelvic pathology because of the previous history or the findings on examination.

There is, however, clear evidence of the diagnostic value of these procedures as indicated in Table VI.

It is important to consider what is the effect of treatment, and lack of it also, on those women without any manifest pathological conditions

TABLE IV

Patients followed up for Two Years from first Visit

	Pregnant	Not pregnant	Total	Pregnant Per cent
Treated	103	289	392	26
Not treated	53	122	175	30
Total	156	411	567	28

TABLE V

Patients followed up for Two Years. Types of Treatment

Type of treatment	Total cases		Pregnancies		Pregnant. Per cent	
	Treated	Untreated	Treated	Untreated	Treated	Untreated
Insufflation	334	233	74	82	22	35
Hysterogram	66	501	11	145	17	29
Biopsy	250	317	61	95	24	30
Hormones	138	429	28	128	20	30
Other forms of treatment ...	111	456	23	133	21	29

TABLE VI
Pregnancy Rates among Patients with Pathological Conditions followed for Two Years

Pathology	Total	Pregnant	Pregnant Per cent
Hysterectomy	1	–	–
Pelvic tuberculosis	11	–	–
Azoöspermia	37	1	3
Tubal blockade	64	6	9
Gross pelvic pathology	16	4	25
Not consummated	11	6	55
Total	140	17	12
Treated	113	16	14
Not treated	27	1	4

because all those with pathological conditions received some treatment, with the exception of 27, whose husbands were proved to have azoöspermia. The number of pregnancies in this group are shown in Table VII.

Thus once again there is no evidence to support the value of treatment, especially as there may well have been many patients with latent pathology who were not treated ($\chi^2=0.4$; $P>.05$).

Effect of Age and Duration of Infertility

This failure to detect any significant difference in subsequent pregnancy rates following treatment may have been due to some selection mechanism operating, by which those least likely to conceive received treatment. This is supported by Table VIII below which shows a difference between the two groups as regards the duration of infertility. Only 39 per cent of the treated group had been infertile for as short a period as 2 years or less, whereas 44 per cent of the non-treated group were in this class.

If allowance is made for this difference by calculating the "expected" number of pregnancies in each group by assuming that the total rate applies to each of the two groups at each duration of infertility, then the percentage of

TABLE VII
Pregnancy Rates among Patients without manifest Pathological Conditions followed for Two Years

	Pregnant	Not pregnant	Total	Pregnant Per cent
Treated	87	192	279	31
Not treated	52	96	148	35

TABLE VIII
Patients followed for Two Years. Distributed by Treatment and Duration of Infertility

Duration of infertility (years)	Treated		Not treated		Standard pregnancy rates per 100	"Expected" pregnancies at standard rates	
	No.	Per cent	No.	Per cent		Treated No.	Not treated No.
1–2	151	39	77	44	36.4	55.0	28.0
3–4	137	35	54	31	24.1	33.0	13.0
5 and over	104	26	44	25	18.2	18.9	8.0
Total	392	100	175	100	27.5	106.9	49.0
Standardized pregnancy rates per 100 women						27.3	28.0
Expected ratio of treated to not treated Per cent							103

TABLE IX
Patients followed for Two Years
Age and Duration of Infertility and Numbers Pregnant

Duration of infertility. Completed years	Age											
	20–24		25–29		30–34		35 and over		Age not known		Total	
	Total cases	Pregnant	Total cases	Pregnant	Total cases	Pregnant	Total cases	Pregnant	Total cases	Pregnant	Total cases	Pregnant
1	20	(10)	28	(13)	15	(7)	9	(5)	–	–	72	(35)
2	42	(10)	61	(20)	34	(8)	18	(6)	1	–	156	(48)
3 and 4	29	(6)	88	(17)	48	(15)	23	(6)	3	(2)	191	(46)
5 and over	5	–	45	(11)	67	(12)	31	(4)	–	–	148	(17)
Duration of infertility	Percentage pregnant within 2 years of observation											
1	50		46		47		56				49	
2	33		33		24		33				31	
3 and 4	21		19		31		26				24	
5 and over	—		24		18		13				18	

pregnancies in the non-treated group would be 103 per cent of those in the treated group. In fact they are 115 per cent; and even in the group without pathological symptoms and who received no treatment they were 112 per cent, which indicates that even after making allowance for the original differences in the two groups there can be no demonstrable therapeutic value in the treatment used. Since this difference is too small to be statistically significant, it may be assumed that there is no effective difference between the two groups.

The Probability of achieving Pregnancy in the Infertile Couple

If this is the case then it is justifiable to amalgamate the 2 groups, and to use them for prognosis when giving advice to women on the chance of pregnancy. Two features appear to be relevant, age and duration of primary infertility. In Table IX the 567 cases are tabulated by age, duration of infertility, and whether a pregnancy was achieved within 2 years. This table suggests that actual age, at least between 20 and 34 years, is of relatively small importance, but the major factor in prognosis is the duration of primary infertility.

This experience, that age is almost irrelevant to the 2-year prognosis, is similar to the results of the study of the total population, as calculated by the last Census on 8th April, 1951 (General Register Office, 1952), where the percentage of married women, not having borne a live-born child, is shown to be almost independent of marriage age between 20 and 34 years, and entirely dependent upon duration of marriage at least until the 5th year of marriage (see Table X). This is, of course, in spite of the fact that nothing can be known about the extent of voluntary infertility in the population at large.

Therefore for the purposes of giving practical advice to a patient seeking an opinion on the probability of achieving pregnancy after one year of infertility, it may be seen from Table IX that her chances within the ensuing 2 years are about 40 to 50 per cent; after 2 years infertility about 30 per cent; after 3 to 4 years 24 per cent; and after 5 or more years 18 per cent; regardless of whether she receives treatment and always

TABLE X
Great Britain. Percentage of Infertile Married Women

Duration of marriage. Completed years	Marriage Age			
	20–24	25–29	30–34	35 and over
0	89	88	88	88
1	55	59	60	75
2	39	39	45	64
3–4	25	28	34	63
5–9	13	19	30	57

providing, of course, there is no manifest pathological condition.

Although these probabilities might appear to be unexpectedly low, further comparison with the 1951 census data shows a marked similarity between our figures and those of the general population as analyzed in the appendix to this article where the figures for conceptions during the first year after attendance are also given.

This similarity is remarkable when it is remembered that our figures are based upon a small selected group of women in the north-east who voluntarily attended a fertility clinic, who were followed for at least 2 years, and where the relevant factor is years of primary infertility, excluding years where there was no opportunity to conceive. The census data, on the other hand, is a random sample of all England and Wales, and is related to years of infertile marriage. The important figures obtained from the clinic and further census data are summarized in Table XI.

The national figures are the result of indirect calculation from a sample of the census data, and are subject to sampling errors as well as any possible inaccuracies of recording, and, of course, include cases of voluntary infertility. Nevertheless, these two series give very similar results where a comparison can be made. The only large difference is during the second year of infertility where the clinic series gives a rate of 49 per cent, and the census data 37 per cent of women who would conceive during the following 2 years. The "expected" number of pregnancies would have been 27 compared with the actual number of 35, an increase of 8.

Discussion and Conclusions

Disappointing results are to be expected in the treatment of infertility. The degree of therapeutic failure demonstrated in the above report, however, is not generally realized. Statistical analysis of the results of work of this kind does not lend itself to the demonstration of individual cases in whom therapeutic success has been achieved. Critical analysis does, nevertheless, show that the number of these individual successes must be exceedingly small.

TABLE XI
Estimated Pregnancy Rates

Duration of marriage. Completed years	Estimated number of first pregnancies per 100 married women from census date 8.5.51		Actual pregnancies per 100 married women from clinic data		Duration of primary infertility. Completed years
	During 1 year	During 2 years	During 1 year	During 2 years	
1	24	37	26	49	1
2	17	29	21	31	2
3	15	26	13	24	3–4
4	13	23			
5	11	20	10	18	5 and over

A statistical agreement of the type shown in Table XI can never be conclusive proof that the two series are related, for it might be that the clinic series may have been depressed by some undetected factor, and raised to the national level by attendance at the clinic, but both series are capable of bearing witness independently of the other. The clinic series are the direct result of careful sieving to exclude irrelevant factors; in this process a considerable percentage were lost, but it is unlikely, particularly in view of the final result, that these women would be more or less fertile than those who were traced.

The question which has been raised by these findings is whether the methods of investigation and treatment of infertility in current use justify themselves. Repeated attendance at the out-patient department, the occupation of beds and the consumption of time, both of patients and of medical staff, expensive prescribing, and the fostering in the patient of a feeling of obligation to persist with time-consuming and profitless treatments seem a wasteful policy in which

both patients and medical attendant appear misinformed as to the chances of ultimate success.

Our techniques of investigation and treatment remain crude and mechanical beside the delicacy of the mechanisms of conception and the numerous factors upon which these processes depend. Nevertheless the detection of certain specific conditions such as azoöspermia, tubal blockade and pelvic tuberculosis has a definite negative prognostic value (see Table VI). These investigations may also bring to light coincident pelvic conditions which require treatment, of which infertility may have been the major presenting symptom. It is suggested, therefore, that, until a significant advance can be claimed in the treatment of this condition, the infertile couple would benefit more from a short investigation completed during the course of one or two outpatient visits, carried out in order to exclude the existence of an absolute barrier to conception. A positive finding would clarify the patient's position with regard to adoption; any clearly defined condition such as rigid hymen or coincident pelvic disease could receive appropriate attention; and in the event of a negative finding the patient could be informed of her chances of ultimate success, for which Table XI might be used as a rough guide.

Summary

(1) About 3,000 patients attended the Infertility Clinic at the Newcastle General Hospital between 1943 and 1952, and it was possible to isolate 1,208 of these who were complaining of primary infertility at the first attendance, and concerning whom adequate information was available.

(2) Where the final result was not known, since the patient had ceased to attend the clinic, a questionnaire was sent to each patient inquiring whether or not they had had a child. Two hundred and seventy-one (34 per cent) failed to reply to this questionnaire, and were lost to the survey.

(3) Of all the patients studied, 255 were known to have had a pregnancy, 21 per cent of the total, or 27 per cent of those remaining after exclusion of 271 who were lost to the survey.

(4) A group of 567 were isolated who had been followed for at least 2 years. 156 (28 per cent) of these became pregnant within 2 years.

(5) There was no difference in pregnancy rates between those who had received some form of treatment, and those who had not, even after making allowance for differences in duration of infertility between these groups.

(6) Between 20 and 34 years of age, actual age appears to be of slight importance in prognosis. The duration of the infertility was the major factor influencing the probability of a future pregnancy.

(7) Data from the 1 per cent sample of the 1951 census are considered so as to get estimates of the probability of conception after a given duration of marriage, and these estimates closely correspond with those obtained from the study of those women who attended an infertility clinic, whether or not they received treatment.

(8) The value of the Infertility Clinic for therapeutic purposes appears to be slight. It is, therefore, recommended that all investigations should be carried out at one session wherever possible to discover any possible pathological condition, and that if such condition is not present then advice and prognosis can now be offered, based upon Table XI.

Appendix

Population Data

The census which was taken on the night of 8th–9th April, 1951, included three questions, addressed to all married women under the age of 50: (*a*) the date of her marriage, and if married more than once, the date of her first marriage; (*b*) the total number of children born alive to her including any who had died; (*c*) whether she had given birth to a live-born child in the period 9th April, 1950, to 8th April, 1951.

A 1 per cent sample of this census data has now been published and, although this does not include the rates at which women of a known age and duration of marriage gave birth to a first live-born child, it is possible to make some estimate of these rates from Table X.3 of the published report.

This table gives the number of married women at ages 15–49 by duration of marriage in completed years whose present size of family is 0 and who, therefore, have never given birth to a live-born child; it also gives the number who bore a live-born child during the year ending 8th April, 1951, and whose present size of family is now 1. The size of the family is defined as "the total number of children

born alive to her". The duration of marriage is estimated from the date of her first marriage, although less than 3 per cent of the whole of this group of women had married a second time. These figures have been abstracted from the Census report and are given in Table A.I below:

CONCEPTION RATES

This data is still not comparable with that obtained from the clinic where the estimated date of conception is taken as the criterion of success whereas the successful termination of pregnancy is used in the Census data.

TABLE A.I

1 per cent Sample of 1951 Census in England and Wales (Table X.3, P.247)
Women aged 15–49 who were married, but infertile during the year preceding the Census

Duration of marriage in complete years on 8.4.51 (i)	Women with no live-born child on 8.4.51 In 1,000's (ii)	Women bearing a live-born child in the year ending 8.4.51, who have only the one child. In 1,000's (iii)	Estimate of women without a live-born child on 9.4.50 (Col. ii + Col. iii) In 1,000's (iv)	Women who bore a first live-born child in the year. (Col. iii Col. iv) per 100 (v)	Duration of marriage in complete years on 9.4.50 (vi)
1	176.5	88.0	264.5	33.3	0
2	122.4	41.8	164.2	25.5	1
3	102.4	24.6	127.0	19.4	2
4	81.7	12.8	94.5	13.5	3
5	62.0	8.9	70.9	12.6	4
6	41.8	5.8	47.6	12.2	5
7	40.8	3.9	44.7	8.7	6

The figures in Col. ii of this table are the number of women who were still infertile at the census date, those in Col. iii are all women who had proved their fertility for the first time during the previous 12 months. Both columns exclude those who had emigrated or who had died during the year, but this is not important as the death rate of married women between the ages of 15–49 was less than 2 per 1,000 in 1950 and the emigration figures were certainly lower than 3 per 1,000 even if all the females who emigrated in that year were married.

Col. iii, however, does not include women who had multiple births or had completed 2 pregnancies in the year, as their size of family on the census day would be 2 or more. Again the total effect of these omissions must be low, as multiple maternities were only about 12 per 1,000.

It is thus permissible to add together Cols. ii and iii to give an estimate of the number of women who were infertile on April 9th, 1950. This is done in Col. iv.

From these figures it is possible to calculate for each year of marriage the number of women, per 100 infertile women, who bore a first live-born child in the year ending 8th April, 1951. This definition should be considered carefully, as it is not the percentage of women who would bear their first live-born child in, say, the third year of her own marriage but is the average of the births amongst a number of marriages, some of which have lasted 2 years and a few days and others may have lasted almost 3 years.

It is possible to make an approximate estimate of the conception rates from the Census data, by assuming that three-quarters of the births in any one year were actually conceived in the previous year. This will underestimate conceptions, as it omits stillbirths which were 2.3 per cent of all maternities in 1950, and abortions which the Royal Commission on Population (1950) estimated at between 7 and 11 per cent of all pregnancies. It will also tend to underestimate the number of pregnancies after a given period of marriage, as rather more than three-quarters of conceptions will take place in the previous year, due to the steady decrease in the rate as the duration of infertile marriages increases.

If, however, this approximation is made and an extra 12 per cent is added to allow for stillbirths and abortions the figures given in Table A.II result.

These estimates from the 1 per cent sample of the Census may now be compared with the clinic data. There were 697 primary infertile women, who attended the clinic and who could be traced a year after the first visit: 110 of these had then become pregnant. Twenty-six per cent of those who had been infertile for only 1 year before the first visit were then pregnant, 21 per cent of those infertile for 2 years, 13 per cent of those infertile for 3 or 4 years, and 10 per cent of those women who had been infertile for 5 years or more.

Age, within the limits of 20–34, had no effect at all upon the probability of conception within the ensuing year.

TABLE A.II
Married Women—Probability of Conception within One Year

England and Wales Census Data			Clinic Data	
Duration of marriage in complete years	Probability of first-born child Per 100	Probability of first conception Per 100	Probability of a conception Per 100	Duration of primary infertility
1	25.5	24	26	1
2	19.4	17	21	2
3	13.5	15	13	3
4	12.6	13		4
5	12.2	11	10	5 and over

CONCEPTION RATES WITHIN TWO YEARS

An estimate can be made from the Census of the number of women who would conceive within a 2-year period after a given duration of infertile marriage: the probability of conception in the first year, plus the probability that those who failed in the first year will succeed in the second.

TABLE A.III
Married Women—Probability of a Conception within Two Years

Census Data		Clinic Data	
Duration of marriage. In complete years	Probability of first conception per 100	Probability of first conception per 100	Duration of primary infertility
1	37	49	1
2	29	31	2
3	26	24	3–4
4	23		
5	20	18	5 and over

This formula has been applied to the pregnancy rate in Table A.II, and gives the results shown in Table A.III.

In the clinic there were 567 women who were followed for at least 2 years, 156 of whom were pregnant within 2 years of their first visit to the clinic. Once again actual age within the range of 20–34 had no effect on the results.

If estimated rates of conception amongst the census population had applied to the 567 women who were followed for 2 years after attending the clinic, then the "expected" number of conceptions would have been 147, which is not significantly different from the actual number of 156.

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THE SIGNIFICANCE OF THE NITROGLYCERINE FLICKER FUSION RESPONSE IN NORMAL SUBJECTS AND IN PREGNANCY

BY

NORMAN MORRIS, M.D., M.R.C.O.G.
Senior Registrar

J. S. TOMKINSON, F.R.C.S., M.R.C.O.G.
Senior Registrar

AND

B. J. O'CONNOR, Grad.Brit.I.R.E.

From the Institute of Obstetrics and Gynaecology
Postgraduate Medical School of London, W.12

THE nitroglycerine flicker fusion reaction has been used in an attempt to diagnose latent pre-eclampsia. The Flicker Fusion Threshold (F.F.T.) can be defined as the minimal number of successive flashes of light at which the light stimulus appears to be continuous and free from flicker. This test has been used by visual physiologists for well over a century but only in recent years has the technique been adopted for clinical investigation. In 1950 Krasno and Ivy described a relatively simple apparatus which could be used for measuring the F.F.T. Using this instrument they claimed to have a method for determining vaso-spasm in the ocular fundus. They make the basic assumption that there is a hypertonus in the retinal vessels in hypertension and in coronary arterial disease which will therefore impair the F.F.T. They claim, furthermore, that this vaso-spasm will tend to be relieved by nitroglycerine, thus improving the visual acuity of flicker. On the other hand, in normal subjects, nitroglycerine is said to impair the F.F.T., due to vaso-dilatation and the resultant passive hyperaemia of the visual mechanism. Krasno and Ivy described the investigation of several patients who were suffering from pre-eclampsia, along with their more complete study of hypertensive disease in general.

Brill *et al.* (1951) followed up this work with a study of the use of the flicker photometer in the pre-clinical recognition of toxaemia of pregnancy. Their results were extremely encouraging, since they claimed to predict the development of toxaemia of pregnancy 2 to 8 weeks before the recognized symptoms and signs appeared. We therefore decided to construct a similar type of Flicker Fusion Meter, which would be at least as accurate as the Krasno-Ivy apparatus, for an independent evaluation of this test in pregnancy.

METHOD

A description of the apparatus which was designed is given in an appendix to this article. Whilst this employs the same principles as the Krasno-Ivy Flicker Photometer, in that a light is interrupted, in our apparatus the light source is a sharply defined square wave interrupted electronically to give a high degree of accuracy which was almost constant over several weeks.

One hundred and eight tests were performed on 74 patients in this investigation. They are divided into pregnant and non-pregnant. The pregnant patients include two groups, namely (*a*) those with a proven hypertension of 140/90 mm.Hg or more and (b) non-hypertensives at term. All the non-pregnant patients were normotensive.

For the test the patient was seated comfortably in a small room, facing the machine which was always in a constant position. The tests were conducted in daylight, the room being free

from glare. Smoking, the consumption of alcohol, or medication with sedatives was not allowed for at least 6 hours before testing. If the subject wore glasses these were also worn for the test. The patient's eyes were 3 feet away from the light source and this distance was kept constant by means of a string attached to the machine. The action of the machine was first carefully explained to the patient. The rate of flicker in all cases was started at 50 per second. The clinician, by slowly rotating the dial, steadily reduced this rate until the patient just noticed the light flickering when she was instructed to say "Yes". As this end point is not easy to appreciate, at least 3 trial runs were allowed and care was taken that the patient called out when she first thought the light was flickering. With these precautions it is remarkable how constant individual results have been. A series of 10 readings at half-minute intervals was then taken, with care to avoid fatigue or conveying to the patient any feeling that she was being "outsmarted" or tricked. A tablet of nitroglycerine, gr. 1/100, was then given to the patient to dissolve sublingually. This usually took about 2 minutes. The subject then often volunteered that she felt hot or faint or had a sudden severe headache. Very few did not notice some effects, and 2 patients fainted. Another series of 10 readings was then taken, and the difference, if any, between the two series of readings was indicated by plotting them as a graph. In our series the majority of patients showed a Flicker Fusion Threshold in the range of 35 to 40 flashes per second. When the F.F.T. readings in the second series are lower than those in the first, indicating impairment of vision, this is defined as a "negative" result and in theory should be the response of a normal subject. If the F.F.T. in the second series is higher, however, this is defined as a "positive" result and again in theory should be the response of a hypertensive or potentially hypertensive patient, due to the relief of pathological vasospasm by the nitroglycerine. These two types of response are illustrated in Figs. I and II respectively. It appears to be generally conceded by the various writers on flicker photometry that there should be an increase or decrease of ½ to 1 flash per second for the test to be considered significant.

Results

One hundred and eight tests were performed on 74 subjects. The results of these are indicated in the following tables.

Table I
Initial Test

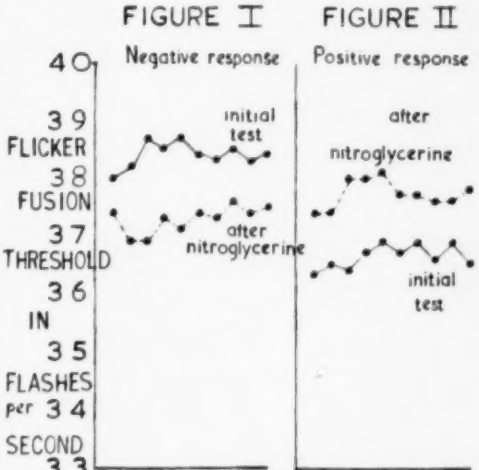
Type of subject	Number Tested	Positive	Indefinite	Negative
Non-pregnant	18	10	4	4
Pregnant normotensive	27	11	6	10
Pregnant hypertensive	29	8	9	12

Table II

Initial Test	Number Tested	Repeat Tests		
		Positive	Indefinite	Negative
Negative	14	1	1	12
Indefinite	7	2	4	1
Positive	13	7	5	1

Table I clearly demonstrates that there was no significant difference in response in any of the groups to support the hypothesis on which the test depends.

Table II is interesting since it shows that a patient's type of response, on the whole, tends



to be constant. This, however, appears of very little clinical significance.

Discussion

If this test is to be accepted as a diagnostic procedure in the detection of early pre-eclampsia it should demonstrate a high degree of specificity when comparison is made between the 3 groups of patients. Our results are at direct variance with those of Krasno and Ivy, and Brill *et al*. who claim that this test may be of value in the early detection of hypertensive disease.

Keys and Simonson (1952) help to confirm our findings in that they were unable to discover any support of the possible value of the nitroglycerine flicker fusion response for the early detection of cardiovascular disease, particularly at the subclinical stage. They state "random guess work would serve equally well". Fox and Wright (1951) also confirm the lack of specificity of the test in normal subjects and those with cardiovascular disease. They also question the basic hypothesis that the test is a sensitive indicator of retinal vaso-spasm and suggest that other mechanisms may be responsible for a positive test. We agree with these remarks. The results of our tests suggest that the nitroglycerine flicker fusion response in itself is not a sufficiently specific method for the early detection of vaso-spasm. Arteriolar hypertonus is generally considered to accompany hypertension, but it is not known which organs are affected first in the natural course of this disease. It is even possible that the retina is not affected until a relatively late stage.

Conclusions

(1) A suitable apparatus has been described for the determination of the nitroglycerine flicker fusion response.

(2) Three groups were tested, namely, normal non-pregnant, normo-tensive pregnant, and hypertensive pregnant patients.

(3) The results obtained gave no evidence that this test is of any value in the early detection of hypertensive disease in pregnancy.

We wish to thank Professor J. C. McClure Browne for his encouragement and help in this investigation.

Appendix

Description of Flicker Fusion Threshold Meter

The requirements to be met by this instrument were as follows:

(1) It should provide a light source capable of being interrupted at any frequency between 28 and 50 cycles per second. (2) The "on" and "off" periods of the source should be of equal duration. (3) The colour of the light should be one readily appreciated by the retina. (4) As it should provide instantaneous build-up and extinction of the light, the plot of light-intensity against time should be a rectangular wave-form. (5) High short-term and good long-term stability were required. (6) The instrument should be robust, portable and easy to operate.

Two alternative approaches were considered; firstly the use of a constant source of illumination with some form of mechanical interruption of the beam. The difficulties in designing a mechanical arrangement of sufficient reliability and reset accuracy together with the complexity required to realize the ideal instantaneous build-up and decay of illumination seemed to indicate the use of a purely electronic system.

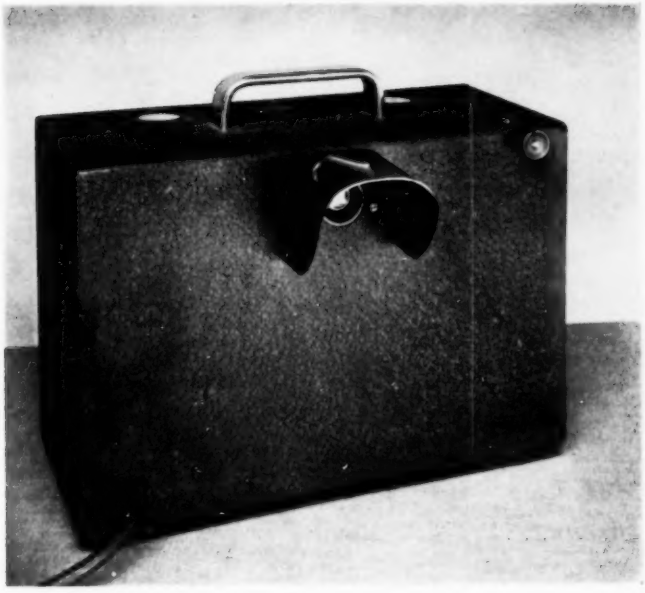
This second scheme involved the use of a variable-frequency oscillator as the frequency-determining element, the output from this, after suitable shaping, being used to switch the lamp via a control valve.

A comparison of the two systems suggested that the latter method provided the simpler solution to the problem, and was capable of adequately fulfilling the requirements set out above.

The final instrument was built into a metal case measuring $12 \times 10 \times 8$ inches. Five valves were used, functioning as follows. A twin-triode (Mullard ECC 35) was used as a phase-shift oscillator to provide a signal variable in frequency between 28 and 50 cycles per second, by means of a single wirewound potentiometer. This signal was fed to another twin triode (ECC 35) the two sections of which were joined in cascade and function as squaring amplifiers. The output from this stage (a positive-going square-wave of unity "mark-space" ratio) was fed to the control-grid of the switching valve (Mullard EL 32). This valve was biased near cut-off, and operated from a 400-volt high tension supply through a suitable anode load resistor. A Siemens pygmy-type neon lamp, joined between the anode of this valve and ground, was used as the light source, and was normally "on". The application of the switching wave-form to the control grid causes the light to be interrupted at a frequency determined by the oscillator. The remaining two valves were a 5U4 rectifier and a VR 150/30 stabilizer.

The colour and light intensity of the neon lamp were found very suitable for the present purpose, and despite the fact that the makers' ratings were exceeded, some months of satisfactory service has been provided by each lamp.

The precautions taken to ensure frequency stability were: (1) the use of high-grade components; (2) care in placement of the critical components forming the



A.

B.

FIG. 3

Two views of the Flicker Fusion Meter showing (A) the light source facing the patient, and (B) the dial for control of the rate of flicker by the clinician.

phase-shift network, in order to avoid changing values due to heating; (3) the use of a well-filtered stabilized H.T. line for the oscillator; and (4) rigid mechanical construction.

An initial warm-up period of 15–20 minutes was necessary, after which there was no noticeable short-term drift. A check on the calibration accuracy after a period of one month's clinical use revealed an error of less than 1 per cent.

Addendum

Since this article was submitted for publication Brill *et al.* (1952) have published a further report of 763 tests on 353 patients. They claim their recent findings confirm the earlier work and gave only 0.89 per cent false negative and 8.4 per cent false positive results in the early recognition of pre-eclampsia. Marty and Hardy (1952) reached somewhat similar conclusions with only 3.3 per cent false negative and 14 per cent false positive results.

We find it difficult to reconcile these findings with those of our own. Admittedly our series was smaller and we employed a slightly different technique. The tests, however, were performed most meticulously, considerable care being taken to exclude those extraneous factors which are known to influence the flicker fusion response. We also consider that our apparatus is certainly as accurate as the Krasno-Ivy flicker photometer.

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THE REMOTE EFFECTS OF CAESAREAN SECTION*

BY

JOHN N. CHESTERMAN, M.B., F.R.C.S.(Ed.), F.R.A.C.S., F.R.C.O.G.

Honorary Obstetrician and Gynaecologist, The Women's Hospital, Sydney

Demonstrator in Operative Obstetrics, The University of Sydney

DURING the past decade, the incidence of Caesarean section has increased, while the immediate maternal and infant mortality following it has markedly diminished. The increasing safety of this operation has widened its indications to such an extent that Leyland Robinson (1951) in a recent William Meredith Fletcher Shaw Lecture, referring to chemotherapy and modern antibiotics, said ". . . obstetrics has been reduced to the simple formula of vaginal delivery with episiotomy and low forceps for normal cases, and Caesarean section for all the rest." If such is the trend of obstetrics, it is well to consider if the patient delivered by Caesarean section suffers any disadvantages from it during her subsequent childbearing life. This paper is an attempt to find this out, by comparing the subsequent history of primigravidae who were delivered by Caesarean section with the subsequent history of primigravidae who had vaginal delivery. To obtain a strict comparison it was necessary that the primigravida who was the control should be of the same age and be delivered of her first child in the same year as her corresponding Caesarean patient. Thus, if Mrs. A., aged 32, had a Caesarean section at her first pregnancy in 1938, it was necessary to find for comparison a primigravida aged 32 who in 1938 delivered her baby *per vaginam*. It was also necessary that each patient and her control should be traced from the records of her first pregnancy without knowing the later history, for to work backwards, say from a fourth or fifth pregnancy to the first, would lend a bias to the findings. All the patients considered had had their first pregnancy between the years 1936 and 1946, so that a period of from 6 to 16 years ago is covered by the investigation. Those of you who have tried to trace patients after so many years, and years including a war, will know the difficulties and, after writing to over 1,000 individuals during the past year, information has been collected from 252 patients, of whom 126 were primigravidae delivered by Caesarean section and the strictly corresponding control group of 126 were primigravidae whose babies were delivered *per vaginam*. I had hoped for a larger number, but some interesting information is derived from these two groups. The remote effects of a Caesarean delivery may be considered in relation to:

(1) Subsequent fertility and fecundity.

(2) Rupture of Caesarean scar in pregnancy and labour.

(3) The patient's subsequent gynaecological history.

The Effect of Caesarean Section on Fertility

An analysis of the subsequent histories of the women in these two groups suggests that there is no difference in their ability to conceive and, having conceived, there is no greater incidence of abortion because of the previous Caesarean section. There were, in fact, more abortions in the control group, possibly because more pregnancies were deliberately terminated by the women in this group. We can conclude that, if the Caesarean mothers subsequently have fewer babies than the others, this must either result from operative sterilization or by their more

* Read at the Second Australian Conference convened by the Australian Regional Council of the Royal College of Obstetricians and Gynaecologists at Melbourne in August 1952.

effective use of contraceptives. In this series the 126 Caesarean patients had 50 fewer babies than their corresponding controls, the exact figures being shown in Table I.

TABLE I

126 Mothers of Caesarean Group	267 Babies. Average 2.1 each.
126 Mothers of Control Group	317 Babies. Average 2.6 each.

This difference between the average number of babies in each group may not seem great, but it is equivalent to the loss of 1 baby to the community with every 2 Caesareans performed.

It is interesting to compare these two groups of patients in succeeding pregnancies and the following graph (Fig. 1) shows the number of pregnancies carried to viability by each group:

The graph shows that delivery of the first child by Caesarean section is no greater deterrent to a second pregnancy than a natural delivery. It is only after the birth of the second child that fecundity falls steeply in the Caesarean group. The reason for this fall is shown in an analysis of the method of delivery of the second child.

As Table II shows, the diminished fecundity after the birth of the second child is related to the method of delivery of this child. A second Caesarean section accompanied by tubal sterilization, of course, ends further childbearing but, of women not sterilized at the second Caesarean, only 1 in 3 had a third pregnancy. In contrast to this limiting effect of the second Caesarean section, observe that the subsequent childbearing of women delivered once only by Caesarean section is almost equal to that of the normal group.

Since so small a number of children are born to women who have had a second Caesarean section, the question, whether the first Caesarean is in itself an indication for the second one, requires careful thought. Also, if a second Caesarean section is performed, should the woman be sterilized? To answer these questions it is necessary to know how the scar in the uterus will be affected by subsequent pregnancy and labour, under what circumstances and how frequently it is likely to rupture, and what are the consequences of rupture.

Since no answer to these questions could be determined from the small series of patients so

FIG. 1

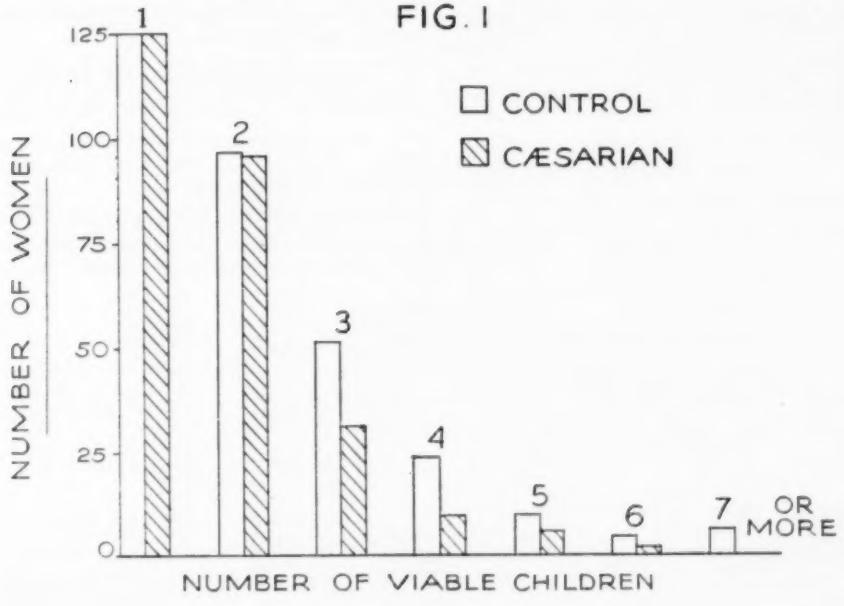

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TABLE II

Caesarean Group

Method of Delivery of 2nd Child		Number of Children subsequent to this
By Vaginal Delivery . .	39	36
By Second Caesarean . . (sterilized 34)	56	10

Control Group

The 96 women who had a second child, had 99 children subsequently.

far discussed, relevant information concerning many more patients has been collected from some large obstetric centres.

The Rupture of Caesarean Scar in Pregnancy and Labour

That a ruptured Caesarean scar is not a common obstetric problem in maternity hospital practice is seen from the data in Table III, which show that, among more than 300,000 women delivered, this complication occurred 40 times, resulting in 2 maternal deaths.

However, any estimate of the frequency of ruptured Caesarean scar is only of value when related to the actual number of women who bore children following a previous Caesarean section. Table IV shows the incidence of rupture among 1,874 such women. The scar ruptured in 33 cases, an incidence of 1.76 per cent. In 14 of the 33 patients the scar ruptured before labour.

Holland in 1920 investigated the results among 448 women who bore children after a previous Caesarean section. In his series there occurred 4 per cent of ruptured scars, a figure that is much quoted. Most of the women were delivered by Caesarean section, and the proportion of ruptured scars to vaginal deliveries was as high as 1 to 4.3. In the series of cases I have collected, the incidence of rupture is less than half that of the earlier one, an improvement that is due to the better surgical techniques and the increasing use of the lower segment operation in the later years.

The third approach to this problem of the ruptured scar is by analysis of the circumstances

TABLE III

Frequency of Rupture of Previous Caesarean Scar

Hospital	No. Deliveries	No. of Ruptured Scars	Maternal Deaths
Women's Hospital, Crown Street, 1940–52	48,784	7	1
3 Dublin Hospitals, 1930–40	92,222	12	1
Margaret Hague Maternity Hospital, 1931–51	117,139	12	0
King George V Memorial Hospital, Sydney, 1945–50	18,124	2	0
New York Hospital Women's Clinic (Cornell University) 1944–50	25,555	7	0
Totals	301,824	40	2

TABLE IV

Incidence of Rupture through a Previous Caesarean Scar

Women delivered either per vaginam or by Caesarean section

	No. of Women Delivered	No. of Scar Ruptures
Women's Hospital, Crown Street, 1949–52	142	0
This series, 1936–46	95	1
New York Hospital Women's Clinic (Cornell University)	943	15
Margaret Hague Maternity Hospital, 1931–51	500	12
Melbourne Women's Hospital, 1940–47	194	5
Total	1,874	33

in which rupture occurred. This information is presented in Table V.

Twenty-three ruptures were through a previous classical scar, and 15 followed the lower segment operation. There is a marked difference in the nature of rupture following these two techniques. Nearly all the classical ruptures were complete, by which is meant, in this context, that either foetus, or placenta or both, had escaped into the peritoneal cavity. In no instance did this happen after rupture of a lower segment scar, although in 1 case the rupture was along the entire length of the old scar. Most lower segment ruptures were small in extent and in many cases the peritoneum was still intact. The different nature of the rupture, depending on the site of the scar, markedly affects the maternal and foetal mortality. The classical scar rupture was responsible for the loss of 2 mothers and 17 infants, whereas no mother died and only 1 infant (a premature neonatal death) followed lower segment rupture.

On the statistical evidence presented here, I consider that it is safe to allow every woman pregnant subsequent to lower segment Caesarean to attempt vaginal delivery, unless of course there is some other obstetric indication for operative interference.

The Patients' subsequent Gynaecological History

With the object of finding out whether more pelvic disorders occurred in women delivered by Caesarean than in those delivered vaginally each patient of my series was asked to describe:

1. Any menstrual disturbances, such as irregularity, heavy bleeding or pain.

2. Any surgical operation performed.

The answers received are summarized in Table VI.

TABLE V

Analysis of 38 Cases of Rupture through Previous Caesarean Scar

(For Source of Cases, see Appendix)

Type of Previous Caesarean Section	Time of Rupture	Type of Rupture		Result			
		Complete	Incomplete	Mother		Child	
				A	D	A	SB
Classical 23	Before Labour 7	7	0	6	1	3	4
	During Labour 16	13	3	15	1	3	13
Lower Segment 15	Before Labour 5	0	5	5	0	5	0
	During Labour 10	0	10	10	0	9	1 (Died)

TABLE VI

	From 126 Women After Caesarean Delivery	From 126 Women After Vaginal Delivery
No. who complained of Symptoms	40	34
Had not had Pelvic Operation	23	17
Had had Pelvic Operation	17	18
Hysterectomy	8	3
Salpingo-oöphorectomy	2	4
Cure of Retroversion	2	3
D. & C.	1	3
Vaginal Cyst	1	1
Sterilization	–	1
Incisional Hernia	1	–
Excision of Abdominal Scar	1	–

Although more complaints were made by the women of the Caesarean group than the controls, the number of women investigated is too small for any definite conclusions. The only marked difference between the two groups is in the incidence of hysterectomy, this operation being more than twice as frequent after Caesarean deliveries than after normal ones.

DISCUSSION

From the evidence collected here it is possible to come to some reasonably valid conclusions.

(1) Diminished childbearing subsequent to Caesarean section is not due to impaired fertility.

(2) Women delivered by Caesarean section may be more prone to pelvic disorders than those who bore children normally, but no definite conclusion can be formed from the small numbers in this report.

(3) The one important disability is the uterine scar which, because of fear that it may rupture, has a restrictive effect on subsequent childbearing. With our present approach to this problem, the restrictive effect is such that of women whose first child is delivered by Caesarean section only 1 in 4 will have more than 2 children. As the evidence shows, this reduction in the size of the family is related to the method of delivery of the second child. If the second child is delivered *per vaginam*, the average number per family approximates that of the woman who had had no Caesarean section.

It is the second Caesarean, frequently accompanied by sterilization (between 50 per cent and 60 per cent are sterilized), that makes the 2-child family, which is undesirable from a social, a national and a biological point of view. Although there is no marked desire for large families in our present form of society, it should be the aim of obstetric practice to avoid procedures that will contribute to the limitation of the size of families below that required to maintain a stable population, unless of course the procedure is necessary to preserve the life or health of the individual concerned.

With the object of stimulating discussion on the foregoing consequences of Caesarean section I put before this meeting three propositions.

(1) The number of first Caesarean sections done can be reduced without increasing maternal or foetal mortality.

(2) With the employment of proper technique at the first Caesarean section, the resulting scar is not an indication for Caesarean section at the next pregnancy.

(3) Only occasionally should the tubes be ligated at the second Caesarean section.

My first contention is supported by a study of the indications given for Caesarean sections, which were performed on 115 patients, all of whom were subsequently delivered *per vaginam*. These 115 patients comprise those women delivered vaginally in Crown Street Women's Hospital in the years 1949–52, and those collected in my series. The previous Caesareans were performed at various hospitals, and the indications given for the previous Caesareans were as shown in Table VII.

Note that 33 per cent were done for what was considered disproportion. From this group, many of the babies subsequently delivered vaginally were the same size or larger than the pre-

TABLE VII
Indications for Caesarean Section

Disproportion	38
A.P.H.	31
Toxaemia	17
Other Indications	29
Total	115

vious Caesarean one and it can be inferred that in many of these cases the trial of labour was inadequate.

The indication "disproportion" is not very precise and certainly has included persistent occipito-posterior positions and/or inefficient uterine action. I agree with Cosgrove (1951) that "Accurate diagnosis and effective treatment of such dyskinesis would cause a considerable drop in the incidence of first Caesarean sections" and I would add that some Caesarean sections performed on young primigravidae for "disproportion" could be avoided by better appreciation of what constitutes a trial labour. It is an unfortunate thing that this operative delivery can be an easy way out of a difficulty for the doctor and at the same time seem the right thing to the patient.

The "Repeat" Caesarean Section

It has been shown that rupture through a lower segment scar is much less frequent than through the vertical upper segment scar; when it does occur it is frequently only a portion of the scar that gives way; it is extremely rare for the infant or placenta to escape into the peritoneal cavity, and finally, that in a series of 15 such cases there were no maternal deaths and only 1 foetal death. It can be asserted that the woman whose primary Caesarean section has been a lower segment one is in no greater danger from vaginal delivery at her next confinement than from delivery by an elective Caesarean section. It must be firmly taught that the lower segment operation is the proper choice in almost every case. The uterine incision should be transverse and it should be sutured with great care. Post-operatively, an "antibiotic cover" and restoration of an adequate haemoglobin value by means of a blood transfusion should be the routine procedure. With the application of this technique the resulting scar no longer becomes a reason for repeating the Caesarean section.

Tubal Ligation

A second Caesarean section is almost certain to be followed by a third, should the patient become pregnant again, and presumably because this is considered an undue risk more than 50 per cent of women are sterilized by tubal ligation at the second Caesarean section. I doubt if a third pregnancy and third Caesarean is an unduly hazardous venture.

Firstly, we should consider: Is there a greater risk of rupture of the scar during a third pregnancy because of the second operative delivery? The surgeon performing the second Caesarean section after examining the uterine scar resulting from the first operation may consider that it is unlikely to stand the strain of a third pregnancy and consequently he may elect to sterilize the patient. On the other hand the second uterine incision can often be made through the scar of the first one, and this scar can be repaired and resutured.

Next, is the risk of a third Caesarean section too great for the patient? In my opinion, it is not, because modern techniques have greatly reduced the immediate mortality of this operation. Sterilization at the second Caesarean section so as to avoid a third operation came into favour at a time when the mortality rate was 4 or 5 times greater than now.

Finally, is it too much to expect a woman to have a third operation? Again, I think not, because modern anaesthesia has greatly lessened the fear of operation in a patient's mind, so much so that many women would prefer an operative delivery to the pains of normal childbirth. For the reasons stated I feel, very definitely, that with a few exceptions sterilization should not be done before the third Caesarean.

SUMMARY

1. 126 primigravidae delivered by Caesarean section had 50 children less than 126 primigravidae selected as controls, who were delivered normally.

2. The diminished fecundity of this Caesarean group was mainly due to "repeat" Caesarean

sections, at many of which tubal sterilization was performed.

3. An analysis of the case histories of 1,874 women who bore children following a previous Caesarean section showed that the scar ruptured in 33 cases, an incidence of 1.76 per cent. Rupture occurred before labour in 14 cases.

4. Rupture of the scar of a lower segment Caesarean section is less frequent than a scar in the upper segment and is not as dangerous to mother or child. In 15 such cases collected, there were no maternal deaths and 1 foetal death.

5. Lower segment Caesarean section is almost always the operation of choice and is not an indication for Caesarean section in a subsequent pregnancy.

6. The question whether tubal ligation is justified at a second Caesarean section is discussed.

The laborious work of collecting information from more than 1,000 women and from the Medical Records Department of Crown Street Women's Hospital was undertaken by Sister M. E. Brown and Miss K. Woolley. My sincere thanks are due to them both.

I also thank the members of the Honorary Medical Staff of the Hospital for permission to use records of their patients.

Appendix

The source of the 38 case histories analyzed in Table IV is:

Royal Hospital for Women, Sydney—Medical Records	4
King George V Hospital, Sydney, 1944–51	2
R. A. Cosgrove, Jersey City, N.J. (Cosgrove, 1951)	12
Arthur L. Wilson, New York (personal communication)	7
This series	1
O'Donel Browne (1951)	1
Crown Street Women's Hospital, 1940–52	7
Author's Private Patient	1
Melbourne Women's Hospital, 1940–47: Medical Records	3
Total	38

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ACTH TREATMENT OF THROMBOCYTOPENIC PURPURA IN PREGNANCY BEFORE TERM

Case Report

BY

A. DE VRIES, M.D., Y. M. BROMBERG, M.D., AND J. GUREVITCH, M.D.

From the Laboratory of Clinical Research, the Department of Obstetrics, and the Department of Clinical Bacteriology, Rothschild Hadassah University Hospital, Jerusalem, Israel

PREGNANCY in patients suffering from essential thrombocytopenic purpura involves a definite risk of mortality to mother and newborn (Robson and Davidson, 1950; McElin, Mussey and Watkins, 1950; Epstein, Lozner, Cobbey, and Davidson, 1950; Whitby and Britten, 1946; Wintrobe, 1946). In order to avoid accidents due to bleeding, splenectomy has been performed during pregnancy up to term (Phythyon and Lartz, 1943; Grossman, 1944; Shipton, 1950; Bernstein, Newman and Hitzig, 1939; Slaughter, Southwick, Falls and Limarzi, 1951) followed by improvement of the haemorrhagic condition in the mother but with considerable foetal mortality. Recently ACTH has been shown effective in the treatment of thrombocytopenic purpura and has been proposed as a preparation for surgery to prevent excessive blood loss (Faloon, Greene and Lozner, 1952). In the case reported here ACTH was given to prepare a patient with thrombocytopenic purpura for delivery.

CASE REPORT

A primigravida, aged 23 years, was admitted to the obstetrical department on 22nd June, 1952, in the 38th week of pregnancy with thrombocytopenic purpura.

Since the age of 10 the patient suffered from bleeding from nose and gums, blue discolorations of the skin and prolonged bleeding following tooth extractions. At her menarche at the age of 13 she had severe uterine bleeding which lasted 1 month. Subsequently menstruation was regular and lasted on the average 7 days with extensive blood loss. At the age of 18 she was admitted to a hospital because of profuse uterine bleeding of 2 months duration for which she received several blood transfusions. The diagnosis of thrombocytopenic purpura was made and splenectomy was proposed but refused by the patient. The patient continued to bleed profusely at each menstruation.

At the age of 22 the patient married. The next menstruation started at the expected time and bleeding continued for 5 weeks. She was admitted to the medical department of the Hadassah Hospital on 1st July, 1951, complaining of weakness and dizziness. The patient was pale and ecchymoses and petechiae were noted on the chest and the extremities. The spleen was palpated deep under the costal margin. There was continuous bleeding from the vagina. The urine was normal. Examination of the blood: Red blood corpuscles 4,420,000 per c.mm.; haemoglobin 6.2 g. per cent; white blood corpuscles 7,000 per c.mm.; thrombocyte counts varied from 64,000–110,000 per c.mm. (method of Rees and Ecker, 1923). The blood smear showed hypochromia, anisocytosis and small platelets. The bleeding time was 18 minutes (method of Duke, 1910), the clotting time 6½ minutes (method of Pohle and Taylor, 1937); there was no clot retraction within 24 hours at 37°C. The capillary fragility test (Ham, 1950) was strongly positive. Plasma prothrombin: 50 per cent (method of Quick, 1942). The prothrombin consumption was slightly disturbed: one hour after clotting there remained 6 per cent prothrombin as determined by the two-stage method (Herz, de Vries and Heiman-Hollander, 1950). The fibrinogen content of the plasma was 360 mg. per cent.

After repeated transfusions splenectomy was performed on 22nd July, 1951. After operation the platelet count rose to a maximum of 280,000 per c.mm., the capillary fragility, the bleeding time, and the clot retraction became normal (see Fig. 1). Menstruation started on 25th July, 1951, i.e., on the 4th postoperative day, lasted 3 days and was normal as to its amount and duration. The patient was discharged from the hospital on 5th August with a platelet count of 26,000 per c.mm. and normal haemorrhagic tests. The platelets were of normal size. She was reexamined on 27th August, 1951, and on 7th September, 1951, when the haemorrhagic tests were still normal but the platelet count had fallen to 140,000–150,000 per c.mm. After discharge the patient had two menstrual periods of normal duration and blood loss, the last one on 25th September, 1951.

The patient was seen in the antenatal clinic in January 1952, when 4 months pregnant. She had no haemorrhagic manifestations until the 5th month of pregnancy when she began to suffer from repeated gingival bleeding and epistaxis. In the 5th month of pregnancy the low platelets value of 30,000 c.mm. was found, accompanied by a positive capillary fragility test, prolonged bleeding time, and absence of clot retraction.

On admission on 22nd June, 1952, the patient was in a good condition, physical findings were not remarkable except for a mild pallor and a few purpuric spots on the chest. The uterus was enlarged corresponding to the 9th month of pregnancy with a foetus in a vertex presentation and normal heart beats. Pelvimetry was normal. The blood-pressure was 115/60 mm.Hg. The urine was normal. Examination of the blood: Red blood corpuscles 3,650,000 per c.mm., haemoglobin 10.5 g. per cent; white blood corpuscles 17,300 per c.mm., thrombocytes 72,000 per c.mm.; clotting time 8 minutes; bleeding time 9 minutes; clot retraction did not appear within 24 hours; capillary fragility test strongly positive. The blood smear showed abnormally small platelets.

On the 4th day of hospitalization she had a profuse gingival bleeding which required tamponade with oxycel gauze.

ACTH treatment was started with the intention to treat the haemorrhagic manifestations in the mother, to prevent excessive obstetrical bleeding at delivery and to try to prevent thrombocytopenic purpura in the newborn, known to occur frequently in children of mothers suffering from essential thrombocytopenic purpura (Robson and Davidson, 1950; Epstein, Lozner, Cobbey and Davidson, 1950).

Beginning on 29th June, 1952, 80 mg. of ACTH (Armour) was administered intramuscularly every day (see Fig. 1). After the patient had received a total of 280 mg. of ACTH and the platelet count had risen to 123,000 per c.mm., the bleeding time, capillary fragility and clot retraction had become normal and no new haemorrhage had appeared. On 2nd July labour began, which after a normal course resulted in a spontaneous delivery of a female newborn, weighing 5 pounds 3 ounces (2,400 g.). No analgesia or anaesthesia was given. The expulsion of the placenta and the immediate postpartum period were accompanied by little bleeding—not exceeding 300 g. The newborn except for its low weight did not show any sign of prematurity. The postpartum period had a normal course; lactation was satisfactory. ACTH administration was discontinued on the day after delivery. The platelet count reached a maximum of 145,500 per c.mm. on 6th July, 1952, haemorrhagic tests being normal. On 15th July, 12 days after cessation of ACTH treatment, the patient had some bleeding on brushing her teeth. The platelet count was found to be 115,000 per c.mm., bleeding time was prolonged, 15 minutes, and the capillary fragility test was positive; the clot retraction, however, was still within normal limits. ACTH was re-administered, again normalizing bleeding time and capillary fragility and with a slight effect on the platelet count. The patient was discharged on 17th July. Re-examination on 27th August, 6 weeks after discharge, showed a platelet count of 114,000 per c.mm., a positive capillary fragility test and delayed clot retraction. Three weeks later the platelet count had dropped to 90,000 per c.mm. and haemorrhagic tests were abnormal; she had some blue discolorations on the legs, but menstrual blood loss was reported to be normal.

The child was born without any purpuric signs. Examination of the blood taken from the umbilical cord revealed: Red blood corpuscles 4,380,000 per

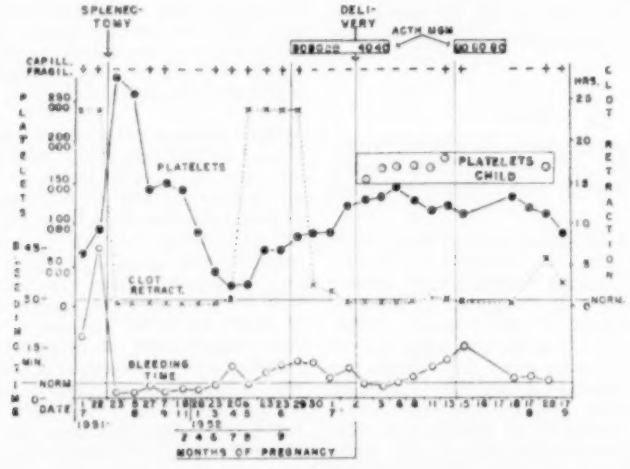

FIG. 1

c.mm., haemoglobin 17 g. per cent; white blood corpuscles 19,350 per c.mm.; thrombocytes 156,000 per c.mm.; clotting time 4 minutes; clot retraction 60 minutes. The platelet count of the newborn taken after cutting the cord was 150,000 per c.mm.; bleeding time was normal. Subsequent platelet levels examined 8 times during the next 2 months varied from 156,000–180,000 per c.mm. (see Fig. 1). The bleeding time was never prolonged and the clot retraction time re-examined on 23rd August, was normal—50 minutes. Plasma prothrombin was not examined as the blood samples clotted on 3 occasions. The child developed anaemia and on 10th July, 9 days after birth, the red blood corpuscles were 3,380,000 per c.mm. and haemoglobin 11 g. per cent. There was no reticulocytosis (0.9 per cent). The white blood corpuscles were 20,150 per c.mm. and the smear showed some anisocytosis and poikilocytosis; no normoblasts were found. There was no jaundice (the blood groups of both the mother and the child were A, Rh_2 Hr+, and of the father A, Rh_1, Rh_2, Hr +; the Coombs test in both the mother's and the child's blood was negative).

The examination of the newborn shortly after birth revealed widened sutures and tense fontanels. The head rapidly enlarged in the course of the following weeks. On 19th August, 6 weeks after birth, the child was admitted to the neurosurgical department with distinct hydrocephalus. The circumference of the head, which at birth was recorded as 30 cm., was now 44 cm. During 12 days daily subdural punctures were done, showing xanthochromic fluid which gradually became lighter in colour and on no occasion showed red cells. On ventricular puncture performed on 1st September, the same brownish fluid was obtained. Ventriculography showed hydrocephalus internus. The diagnosis of congenital hydrocephalus and old ventricular bleeding was made and the child was discharged from the hospital on 4th September. No purpuric manifestations were noted in the child during the whole period of observation, extending over 2 months following delivery.

Comment

When facing the problem of management of pregnant patients suffering from idiopathic thrombocytopenic purpura, one has to consider the considerable maternal and foetal mortality involved. In fact about 10 per cent of the mothers will die from the haemorrhagic complications of the disease, the majority of newborns will present purpura at birth or shortly thereafter, while more than 25 per cent of the children will either be delivered stillborn or die within 3 days after birth (Robson and Davidson, 1950). There is no consensus of opinion as to whether pregnancy constitutes an aggravating factor in the course of thrombocytopenic purpura. While some authors claim that pregnancy may lower the blood platelet level and increase the tendency to haemorrhage, the majority oppose this view and consider the high maternal mortality as that expected in the normal course of the disease. In our patient an extensive fall in platelets accompanied by haemorrhagic manifestations occurred in the 5th month of pregnancy, 7 months after splenectomy. Whether this relapse was induced by the pregnancy or would have occurred independently cannot be decided.

The thrombocytopenic purpura in children of thrombocytopenic mothers is a self-limited disease and if not fatal recedes spontaneously within a few days or months after birth. It has been suggested that a factor inducing thrombocytopenia, circulating in the blood of the mother (Harrington, Minnich, Hollingsworth, and Moore, 1951), is transmitted through the placenta and causes temporary thrombocytopenia in the child (Epstein, Lozner, Cobbey, and Davidson, 1950).

Splenectomy performed in thrombocytopenic purpura during pregnancy, although improving the condition of the mother, seems not to solve all the problems involved as the newborn still may suffer from thrombocytopenic purpura and the foetal mortality following splenectomy is considerable. Moreover there remains the problem of thrombocytopenic purpura occurring in pregnancy in previously splenectomized women, as in our patient.

ACTH has been shown to raise the platelet level and to normalize bleeding time, clot retraction and capillary fragility in thrombocytopenic purpura (Wintrobe *et al.*, 1951). In our patient ACTH administered for 5 days beginning 2 days before delivery raised the platelet count, normalized the haemorrhagic tests and controlled the haemorrhagic manifestations; the patient delivered with little blood loss. Recurrence of purpura 12 days after cessation of ACTH treatment was again controlled by ACTH administration, showing both the effectiveness and the temporary action of ACTH.

The question may be asked whether ACTH administered to pregnant patients with thrombocytopenic purpura may prevent the disease in the newborn. In the case reported above the

hydrocephalic child never did present the haematologic syndrome of thrombocytopenic purpura. However, the xanthochromic fluid obtained by ventricular puncture indicates that cerebral haemorrhage had occurred. Whether this haemorrhage occurred before delivery and ACTH treatment or thereafter cannot be decided. Had ACTH not been administered the chance that thrombocytopenic purpura might have occurred in the newborn in our case is high. Robson and Davidson (1950) reported that, out of 9 patients submitted to splenectomy and suffering from recurrence of thrombocytopenic purpura during pregnancy, 8 delivered babies with purpura. ACTH might be effective against thrombocytopenia of the newborn either by neutralizing a thrombocytopenic factor in the blood of the mother, or by acting directly on the foetus, after passage through the placenta. Up to now no evidence is available as to the transmission of ACTH through the placenta. However, transmission is plausible, as ACTH in human plasma has been shown ultrafiltrable (Rossi, Montanari, Martinelli and Moruzzi, 1952).

ACTH treatment seems to us of special importance in thrombocytopenic purpura associated with pregnancy, since the temporary improvement achieved may allow us to carry the pregnancy to the end and postpone splenectomy. ACTH should be administered in pregnancy during the periods when haemorrhagic phenomena appear and as a rule before term in order to prevent excessive bleeding, which may occur in the third stage of labour, after delivery and from operative wounds connected with obstetrical management. ACTH treatment before term may possibly also prove of importance in the prevention of thrombocytopenic purpura in the newborn. No harmful side-effects have been observed following ACTH treatment in usual doses in pregnant women (Ferguson, 1951).

Summary

In a patient suffering from essential thrombocytopenic purpura, treated by splenectomy, purpuric manifestations recurred during pregnancy. ACTH was administered before term with a view to treatment of the purpura of the mother and to prevent haemorrhagic accidents related to thrombocytopenia, which might occur during delivery. The haemorrhagic manifestations in the mother disappeared under ACTH treatment with normalization of the haemorrhagic tests. Labour delivery and the postpartum period ran a normal course. The newborn presented tense fontanels and developed marked hydrocephalus subsequently. Subdural and ventricular punctures revealed xanthochromic fluid. Examination of the umbilical blood and repeated examinations of the blood of the child did not show thrombocytopenia or other abnormal haemorrhagic tests.

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TONIC CONTRACTION OF THE UTERUS

Two Unusual Cases

BY

JAMES BAXTER, M.D.

Rankin Maternity Hospital, Greenock

KERR and Moir (1949) state that "Tonic contraction of the uterus is a condition observed in cases of pronounced dystocia in which the uterus has for long tried to overcome the obstruction to expulsion of the child. It is observed, therefore, in marked degrees of pelvic disproportion, impacted shoulder presentation, hydrocephalus, malposition of the head, etc.; it is also encountered when ergot or pituitary extract is injudiciously administered." They cite as important features of tetanic contraction constant pain, discomfort, and great restlessness together with a uterus uniformly convex and tender to pressure. Berkeley, Bonney and MacLeod (1938), describe a condition which seems to differ only in degree from that of tonic uterine contraction. They name this "Irritated Uterus" and believe that it is much more common than tonic contraction. The chief difference between an "irritated uterus" and tonic contraction would seem to be that in the former condition intermittent uterine contractions continue to occur.

All authors stress the aetiological factors as falling into one of three main groups. (1) Obstruction to descent of the foetus. (2) Intra-uterine manipulations including forceps attempts to deliver. (3) Injudicious use of ecbolic drugs. The writer has been unable to find any reference in the literature to tonic contraction of the uterus, *sui generis*, as it were, and occurring without any apparent causative factor. The following case histories demonstrate that tonic contraction of the uterus can occur in circumstances which render its occurrence inexplicable in the usual terms.

CASE 1

Miss McK. was admitted to the Rankin Maternity Hospital at 12 noon on 10th April, 1952, as a case of face presentation and intra-uterine death of the foetus. The patient was an unmarried primigravida aged 19 years. She was of good physique and in good condition. According to her dates her pregnancy was at term. She was in labour and contractions were estimated as fair in strength and duration, and occurring at 7-minute intervals. The size of the abdomen was consistent with a full-time pregnancy, although the foetus was on the small side. The head was in the pelvis and the foetal heart sounds absent. On vaginal examination the cervix was found to be taken up and the os 3 fingers dilated. The membranes were found ruptured and an anencephalic head palpable. As her pains became more distressing she was given 100 mg. pethidine intramuscularly. At 3 p.m. of the same day she was fully dilated and bearing down. At 6 p.m. she was still undelivered despite strong contractions and good downbearing efforts during these 3 hours. She was now obviously distressed, restless, and complaining of continuous pain in the abdomen and lower back. The uterus was strikingly pyriform in shape and uniformly hard to palpation. This hardness, undoubtedly due to a state of high muscle tone, was continuous, and although superimposed contractions could not be detected by the hand yet she appeared to experience an intermittent pain which she distinguished from the continuous pain and to which she responded by bearing down. In the presence of constant pain and distress it was difficult to gauge uterine tenderness to palpation but it was not marked. Despite these observations tonic contraction was not thought possible in the absence of any obstruction. The only drugs administered were pethidine, and nitrous oxide delivered over a standard Minnitt's apparatus. Signs of impending exhaustion were now apparent in her flushed, dry-lipped appearance, and increasing pulse rate. It was decided to examine her thoroughly under anaesthesia and to deliver her, if possible, by taking down and making traction on an arm—a fairly easy manipulation when an anencephalic head presents and the os is fully dilated. The head was found in the pelvic cavity and the os was fully dilated. The pelvis was not contracted and there was no obstruction. When an attempt was made to introduce a hand above the head to bring down an arm the wall of the uterus was found to be so closely and tightly applied to the

shoulders of the foetus as to make any manipulation impossible. It is not uncommon to find the uterus in some degree of spasm during light anaesthesia, and the anaesthetist was asked to deepen the anaesthesia. When he was satisfied that she was quite relaxed examination revealed no change in the uterine tone. The anaesthetist now changed over from nitrous oxide, oxygen and ether, to chloroform on an open mask without any effect on the uterus, although at one stage the anaesthesia was very deep. It was difficult to know what to do in these circumstances, but it was felt that we should deliver her there and then, rather than run the risk of having to repeat the anaesthetic and do a difficult job when her general condition would be poorer. The easiest solution was Caesarean section, but, in a case such as this, a confession of obstetrical impotency. Attempts were now made to pull the foetus down by traction on the head, and, although a variety of instruments was tried, traction resulted only in the avulsion of the slightly macerated tissues. It was only after decapitation that a powerful grip was obtained over the upper part of the chest wall with two pairs of heavy forceps. Traction now brought the right axilla within reach so that a finger could be hooked into it and the arm brought down. Traction on the arm failed to deliver the shoulders although the left axilla was brought far enough down to allow the other arm to be delivered. Strong traction on the arms delivered the trunk to the level of the costal margin but not before one arm began to tear away. The macerated skin made traction difficult and eventually the abdominal cavity was opened into along the costal margin to allow evisceration. With the hand in the abdominal cavity of the foetus it was possible to feel the close embrace of the uterine wall. At the same time the anaesthetist, who had been helping with a little fundal pressure, stated that the uterus was as hard as ever, and still remarkably pyriform in shape. The buttocks were very difficult to deliver and it was just a question whether their bulk would have to be decreased in some way when a last despairing traction effort brought them away. The placenta followed the buttocks immediately and there was no bleeding. An episiotomy had been performed to allow greater safety in manipulation, and although no instrument had been introduced into the uterine cavity, and traction—limited in any case by maceration of the tissues—had been exerted with due regard to the possibilities, nevertheless a hand was introduced to explore for injury. The uterine cavity was almost obliterated but two fingers could be forced into it. The walls were hard and retracted, there was no bleeding and no sign of injury. Although this patient had been deeply anaesthetized for 90 minutes, and much of the anaesthetic chloroform, her pulse and general condition were still good. She was given 550 ml. of intravenous glucose saline as some protection against liver damage. She made an uneventful recovery and was discharged well on her fourteenth day.

There can be no doubt that this was a case of tonic contraction of the uterus corresponding to the type of "irritated uterus" described by Berkeley, Bonney and MacLeod. This condition of tonic contraction involves the uterus as a whole—from fundus to os externum—and the lower segment is equally involved. When the uterus, in spasm, maintains its pyriform shape, follows down its diminishing content, and so resists the extraction of every inch of the foetus, then delivery from below is bound to be difficult indeed, and one can readily understand what the obstetricians of last century meant when they described this condition as "active retention of the foetus". Tonic contraction is sometimes seen in cases of shoulder presentation and delivery is easily accomplished by traction on the arm following decapitation because the transverse lie of the foetus and the extreme stretching of the lower segment prior to the onset of spasm prevent the uterus from assuming its pyriform shape, thus obviating the "bottleneck" effect.

CASE 2

Mrs. S. was admitted to the Rankin Maternity Hospital at 3 a.m. on 12th August, 1952, as a case of eclampsia. According to her doctor, she was a primigravida, aged 24 years, and due in 2 weeks. The toxaemia had developed rapidly. The day before admission the blood-pressure was 150/100 and the urine free from albumen. There had been 2 typical eclamptic seizures before admission.

On admission she was found to be a woman of poor physique and mentally confused. She had another fit before any examination could be made. Morphine gr. ¼ (16 mg.) and 6 ml. paraldehyde were given intramuscularly while a solution of Bromethol was prepared for rectal administration. This therapy succeeded in controlling the fits. Subsequent examination found her B.P. 180/120 and albuminuria 4 parts Esbach. The foetus was estimated to be about 6 pounds (2,722 g.) in weight and the heart sounds were recorded at 130 per minute. The head was engaged in the brim. Twelve hours after the cessation of fits a vaginal examination was made. The pelvis was found to be normal, and, as the cervix was "ripe", the membranes were ruptured with the Drew Smythe catheter. Labour pains began late that night and on the following morning uterine contractions were strong and frequent. At 10 a.m. the foetal heart sounds were reported to be slowing down and irregular. Seen at this time she was flushed and anxious-looking, and complaining of continuous pain in the lower back and in the abdomen. She had recovered from the effects of the eclamptic fits and the heavy sedation required to control them, and

answered questions intelligently. She was restless and obviously greatly distressed by the pain which was not relieved by pethidine 100 mg. intramuscularly. The uterus seemed very compact and erect, and its pyriform shape was notable. It was uniformly hard to palpation but not remarkably tender. Although she was bearing down from time to time, no contraction could be felt to be superimposed upon the spastic muscle. The foetal parts were not palpable and the F.H.S. were recorded at 80. Vaginal examination found the head in mid-cavity and lying transversely with the occiput to the right and the vertex presenting. As the os was fully dilated it seemed that delivery with forceps would be safe and easy. When she was anaesthetized an episiotomy was performed and a hand introduced to correct the position of the head and to locate the cheek along which the first blade would be laid. It was then found that the lower edge of the uterus, corresponding to the external os, was so tightly clasped about the head that it was impossible to introduce the fingers between them. The anaesthetist deepened the anaesthesia to the limit of safety without any apparent effect upon this spastic condition. It was now obvious that the uterus was in tonic contraction and that instrumental delivery would be extremely dangerous. We were reluctant to resort to Caesarean section, especially as the viability of the foetus had not been improved by the quantity and variety of sedative drugs administered, apart from the effects of the toxaemia and a deep ether anaesthesia. The anaesthetic was stopped and it was decided to try the effect of sedative and spasmolytic drugs. Meantime glucose-saline was administered by intravenous drip and, when she had regained consciousness, she received ¼ gr. morphine by subcutaneous injection. The acute phase of her toxaemia had passed, her urinary output was satisfactory in the circumstances, and it was felt that recurrence of fits was unlikely—especially as anti-convulsant drugs were being administered. Her general condition was fairly good but it was appreciated that delivery could not be indefinitely delayed and preparations were made for immediate delivery by Caesarean section should her condition begin to deteriorate. Although pain was now less distressing morphine and pethidine failed to reduce the tone of the uterine muscle, and, late in the afternoon, her condition was apparently unchanged. The foetal heart sounds had improved soon after the induction of anaesthesia but continued irregular up to the time of delivery. The consultant obstetrician for the County of Renfrewshire, Dr. W. G. Mackay, saw her about 6.30 p.m. He agreed that abdominal examination suggested tonic contraction of the uterus, and, when the patient was again anaesthetized and examined *per vaginam*, he confirmed our findings and suggested Caesarean section as the safest method of delivery. She was immediately taken to the theatre where the operation was performed by Dr. Mackay. When the abdomen was opened the only abnormality noted was the pallor of the uterus although this was not marked. There was no undue stretching of the lower segment and the peritoneal reflection was at a normal level. Neither a retraction ring nor a constriction ring was visible or palpable. The lower segment was opened through a curved transverse incision and the foetus easily delivered. The placenta followed immediately and the operation from first to last was comparatively bloodless. The most remarkable feature was the behaviour of the incision following delivery of the placenta. The upper and lower edges became everted, the angles tended to be indrawn, and the appearance was that of a pair of pouting lips. The infant, a female weighing 6 pounds 2 ounces (2,779 g.), took some time to come round but eventually did well. A ring of contusion encircled the scalp along the sub-occipito bregmatic circumference and was clearly due to the clasp of the os externum. Mother and infant were discharged well on the eighteenth day of the puerperium.

Here again there can be no doubt that we were dealing with a case of tonic contraction of the uterus. A postnatal X-ray pelvimetry report confirmed a normal gynaecoid pelvis. It is difficult to explain the survival of the foetus when the uterus is believed to be in a condition of prolonged tonic contraction. It was noted that the heart sounds began to improve soon after the induction of anaesthesia and it may be that enough relaxation was induced by the anaesthetic to allow the utero-placental circulation to continue at a level sufficient to sustain foetal life. The continued irregularity of the sounds indicated that the circulation was being maintained precariously.

One can only guess at the aetiology of tonic contraction in these 2 cases but some analogy to constriction ring is possible. Constriction ring dystocia is a well-known clinical entity (White, 1913). Constriction rings produce true spastic strictures of the uterine cavity because an annular zone of muscle goes into local tetanic contraction and forms a tight constriction about some part of the foetus. Clinically this condition does not present the same urgent features as does tonic contraction, although, in diagnosis and treatment, it may present a more formidable problem. The aetiology of constriction ring is obscure and theories postulate some special sensitivity of the neuro-muscular mechanism and/or the presence of some noxious or irritating agent. However it may be, it seems reasonable to suppose that, in some cases, not only a seg-

ment, but the entire uterine muscle is susceptible to the action of the activating factor so that tonic contraction is produced instead of a constriction ring. It is, in fact, easier to imagine the operation of an irritant as affecting the whole muscle rather than an isolated annular segment. In both of these cases labour progressed normally into the second stage. Both were obstetrically abnormal at the outset but the abnormalities were such as we have seen often without any development of tonic contraction.

It is easy to miss the diagnosis when the mind is convinced that there is no reason for the condition which the eye and the hand suspect.

I am indebted to Dr. W. G. Mackay for his advice and assistance.

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BREECH DELIVERY OF A LARGE FOETUS

BY

JAMES BAXTER, M.D.

Rankin Memorial Hospitals, Greenock

A LARGE FOETUS presenting by the breech is always a formidable problem and many authorities suggest that this complication should be avoided by induction of premature labour when version fails. Higgins (1942), discussing this subject, writes, "Of the factors which may ensure smooth progress, without any hitch in expulsion, smallness of the foetus must be placed first. This applies especially to primiparae in whom the very fatal complication of high impaction may develop if the child is large and in whom the much less serious but nevertheless disturbing arrest of the breech at the vulva is so common."

Any considerable experience of breech delivery will afford ample evidence that this thesis which relates difficult delivery to foetal weight is substantially true, but, in the writer's experience, it is more so in the case of the multipara, and particularly in the woman of high parity whose infants step up their birth weights, as it were, in a sort of arithmetical progression. It has never been found necessary to induce labour in a primigravida merely because of breech presentation. It has, indeed, been a rare experience to find a large foetus presenting by the breech in a primigravida and in a series described by the writer some time ago (1949) the average weight was 6 pounds 14 ounces (3.1 kg.) and the heaviest infant weighed 9 pounds (4.1 kg.). On the other hand, it has been thought wise to induce labour in some multiparae when the foetus was considered large enough and version failed.

The estimation of foetal weight in the antenatal period is never very easy but it is usually possible to estimate that the foetus is large enough and mature enough to survive. The optimal weight for breech delivery is probably about 8 pounds (3.6 kg.).

The following case history presents interesting features.

Mrs. B. was admitted to the Rankin Maternity Hospital on 5th December, 1951, with a history of having been fully dilated for at least 2 hours with non-engagement of the breech. The patient was a tall, well-nourished woman, aged 40 years, para-9, and in good condition. She was 9 days overdue. Her last 4 confinements were conducted in this hospital. The first of these, in 1945, the writer terminated by forceps while the other 3 went on to spontaneous delivery. The infants weighed from 8½ pounds (3.9 kg.) to 10 pounds 10 ounces (4.8 kg.). Abdominal examination found a breech presentation. The foetus was considered large and the weight estimated at about 10½ pounds (4.8 kg.). The foetal heart-rate was 140. Uterine contractions were occurring at 7-minute intervals and were of moderate strength and duration. Vaginal examination found a loose cervix with oedematous anterior and posterior lips. The os easily admitted the half-hand. The breech was presenting and not engaged. The legs were extended and the foetal sacrum was directly posterior. The membranes were ruptured and meconium stained liquor draining away.

The oedema of the cervix was thought to be due to too early bearing-down efforts and, although the foetus was large, the pelvic examination and obstetrical history suggested that breech delivery should be allowed in preference to Caesarean section. Meantime it was hoped that the breech would come down if the oedema subsided and the os allowed to reach full dilatation. The patient was instructed not to bear down with her pains and was given 100 mg. of pethedine intramuscularly, which was repeated in 4 hours.

Twelve hours after admission vaginal examination found an oedematous mass about the size of a large orange occupying a position consistent with an oedematous lip of cervix but further investigation showed this to be the oedematous foetal scrotum. The os was fully dilated and it was decided to bring down a leg. The vagina was so distensible that the whole hand could be introduced without causing the patient any discomfort and it was considered possible to perform the manipulation without resort to general anaesthesia. She was put over in the left lateral position, and, by means of Pinard's manoeuvre, the right foot was reached and brought down very easily. It was now obvious that the foetus was a large one indeed, and the sight of this gargantuan limb stirred some unhappy memories. Uterine contractions now became stronger. The patient was put up in the lithotomy position and

encouraged to bear down with her pains. Very soon the breech was born, the left leg coming down fully extended along the trunk. No attempt was made to force or to hurry the delivery. With delivery of the breech the trunk had rotated but despite strong bearing-down efforts she could not deliver it beyond the inferior angles of the scapulae. A hand was introduced and the arms found to be extended. With the help of the patient's own bearing-down efforts the trunk was drawn down and rotated until it was found possible to reach the posterior arm and up beyond the elbow so that it could be safely disengaged. The anterior arm could not be reached under the symphysis nor could it be rotated into a posterior position—probably because of the great breadth of the shoulders. With the shoulders lying transversely, however, and the trunk pushed well back, it was found possible to pass the fingers over the shoulder and to follow the arm up to the elbow, when it was successfully brought down without undue force. The after-coming head was expelled with great rapidity, and rather unexpectedly, by a single down-bearing effort. The infant cried at once and the third stage was normal. No episiotomy was performed and there was no laceration. Mother and infant were discharged well.

The infant, a male, weighed 14 pounds 2 ounces (6.4 kg.) and the bi-parietal diameter of the head measured 4½ inches (10.47 cm.). The length from heels to vertex measured 24 inches (61 cm.). The bi-sacromial diameter was 6½ inches (16.5 cm.).

Discussing this case with the county consultant, Dr. W. G. Mackay, he suggested that this patient must have a very efficient type of pelvis and that X-ray pelvimetry would be of great interest. This report was as follows:

Obstetrical conjugate 11.4 cm. (4.44 ins.). Available transverse 12.7 cm. (5 ins.). Lower antero-posterior 12.3 cm. (4.81 ins.). Bi-spinous 9.8 cm. (3.81 ins.). Post-sagittal 8.8 cm. (3.44 ins.). Sub-pubic angle 70°. Gynaecoid brim.

These measurements are no more than average. The sacrum was well curved and short but the sub-pubic angle surprisingly narrow.

The factors which determine success or failure in breech delivery are many and varied from case to case, but consideration of these measurements, together with the pelvic shape, allows some assessment of the parts played by the bony pelvis and the soft tissue resistance respectively when after-coming head dystocia occurs in the so-called uncomplicated breech case.

Soft tissue resistance to the expulsion of the after-coming head is represented not by an imperfectly dilated cervix, which is, in fact, rare when the full-time frank breech is spontaneously delivered, but rather by the vagina and its muscular supports, and is always greater in the primigravida. Moreover, in breech cases, the "streamlining" of the foetus is directed the wrong way round so that the frictional resistance is increased and extension is the favoured movement. The margin of safety allowed by the average bony pelvis must be very considerable to afford the fairly easy passage of a foetus nearly twice the weight of the average and a bi-parietal diameter nearly ½ inch (1.27 cm.) greater than average. The bi-parietal diameter of the normal full-time head never exceeds 4¼ ins. (10.8 cm.) and very rarely does it reach this maximum; nor is this diameter always related to the weight of the foetus (Baxter, 1949). The diameter of engagement of the fully flexed after-coming head, therefore, finds ample accommodation at all levels during its transit through the average bony pelvis. As foetal weight falls below 8 pounds (3.6 kg.) the circumference of the frank breech diminishes more rapidly than the circumference of the head. If the pelvis is normal and the foetus normal difficulty never arises because the head is too large relative to the bony pelvis but rather because the breech is too small to dilate the required passage through the soft tissues. At first sight it would seem that the small head of the premature foetus would meet with less resistance, but this gain is offset by the smaller breech which fails to prepare an easy passage for the head. In these circumstances the head must make its own passage, and, since the premature head does not readily withstand compression, cerebral injury is more easily sustained. On the other hand, as weight increases above 8 pounds (3.6 kg.) the circumference of the frank breech grows in excess of the circumference of the fully flexed head, as do the circumferences of the shoulders and thorax, and when the foetus exceeds this weight it is probable that more difficulty is experienced with extended arms than with the after-coming head. Even a large breech may not smooth the way for excessively broad shoulders and a bulky thorax which so fill the pelvic cavity that the arms are forced to extend, and which so distend the vagina that even with an episiotomy it is extremely difficult to reach the arms and to effect their disengagement. In a general way it may be said that as weight

falls below 8 pounds (3.6 kg.) the more is aftercoming head dystocia to be feared in the primigravida, while as weight increases above 8 pounds the more are extended arms to be feared in any patient.

The frank breech would seem to occur much more frequently than the complete breech, particularly in primigravidae, and, as its circumference is greater than that of the complete breech, it acts as a more effective dilator. Figures quoted by Pomerance and Daichman (1952) show that complete breech results in a definitely increased foetal loss as compared with frank breech, and it may be for the above reason.

Extension of the head introduces a different problem because the increased diameter of engagement produces what amounts to disproportion between the head and the bony pelvis. It is well known that extension may be induced by attempts to overcome soft tissue resistance by traction on the trunk of the foetus.

An interesting corollary to these observations is that moulding of the foetal head in vertex presentations is an adaptation to soft tissue resistance rather than to resistance of the bony pelvis (Baxter, 1949).

By and large, breech delivery gives rise to little trouble except in a small number of cases but these are the more interesting because they offer the greater challenge to the technician. The factors which determined the successful issue of this case were quite fortuitous. The patient was most co-operative, and the easy distensibility of her soft tissues, combined with her fortitude, allowed manipulation without resort to anaesthesia of any kind. Thus uterine force and ability to co-operate remained unimpaired throughout. This happy ending does in no way detract from the recommendations of Higgins in so far as the multipara is concerned, and it is probably true that the greatest good for the greatest number will only be obtained by external version or induction of premature labour in those cases where a large foetus, presenting by the breech, is to be feared.

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VAGINAL RECURRENCES IN CARCINOMA OF THE BODY OF THE UTERUS AND THEIR PREVENTION BY RADIUM THERAPY

BY

B. M. WILLMOTT DOBBIE, M.A., M.B., F.R.C.S., D.M.R.E.

Surgeon, The Birmingham and Midland Hospital for Women

THE work about to be described was suggested by the clinical observation that vaginal vault recurrences are rather common when carcinoma of the body of the uterus is treated by hysterectomy alone, but not when radium therapy is used instead of surgery. The term recurrence is here used to include all scar recurrences and typical metastases.

In 1936 the writer began to treat the vaginal vault with radium after hysterectomy, and this procedure has been in use ever since, with a later modification to include the entire vagina.

MATERIAL

From 1936 to 1947, 84 patients were so treated. These are compared with 64 cases treated by hysterectomy only and 18 in whom hysterectomy was followed by X-ray therapy to the pelvis. All were patients in the gynaecological departments of the General, Women's, and Queen Elizabeth Hospitals, Birmingham, now parts of the United Birmingham Hospitals. Every case receiving radiotherapy was recorded and followed up; those treated by surgery only were not followed up at the Women's Hospital before 1943, so earlier surgical cases from this source are excluded to avoid any accidental selection.

The 224 cases considered had all an adenocarcinoma in the body of the uterus, all naked-eye evidence of the disease was successfully removed, and all the patients were free from demonstrable recurrence, local or distant, 3 months after operation. Thus, these patients all had a fair chance of cure and any superiority in one method of treatment should show in the 5-year results. No case was lost sight of during the follow-up; those few who died of intercurrent disease are excluded. There was no controlled plan of treatment; whether patients were treated surgically only or referred for X-ray or radium therapy after hysterectomy depended on the inclination of individual surgeons; some sent none of their patients, others some of them, others all. The three treatments were in use throughout the period. As will be seen later, there is some evidence to suggest that there was a tendency for more advanced cases to have supplementary treatment.

The writer was responsible for about 15 per cent of the hysterectomies and the whole of the radium therapy.

TECHNIQUES

All the operations were total abdominal hysterectomies. It was usual to suture the cervix before operation, but this may not have been done in every case. The tubes and ovaries were always removed, except in a few instances where the condition was found only on opening the uterus after operation.

The doses of X-ray delivered to the pelvis, and the techniques used, varied considerably through the years. A detailed account of them is unnecessary here, but, for the purpose of the discussion, it is important that at no time did the planned treatment include a significant dose to the vagina. Radium treatments were given 3 to 4 weeks after hysterectomy.

The method of applying the radium has also changed. At first a Stockholm box was used, giving to the vault in one treatment about half the standard vaginal dose for carcinoma of the cervix. Later, the routine was a full dose by means of the Paris colpostat. Lastly, after two recurrences were observed at the introitus, it was decided to irradiate the whole vagina. Twenty-four of the 84 cases were treated in the last way.

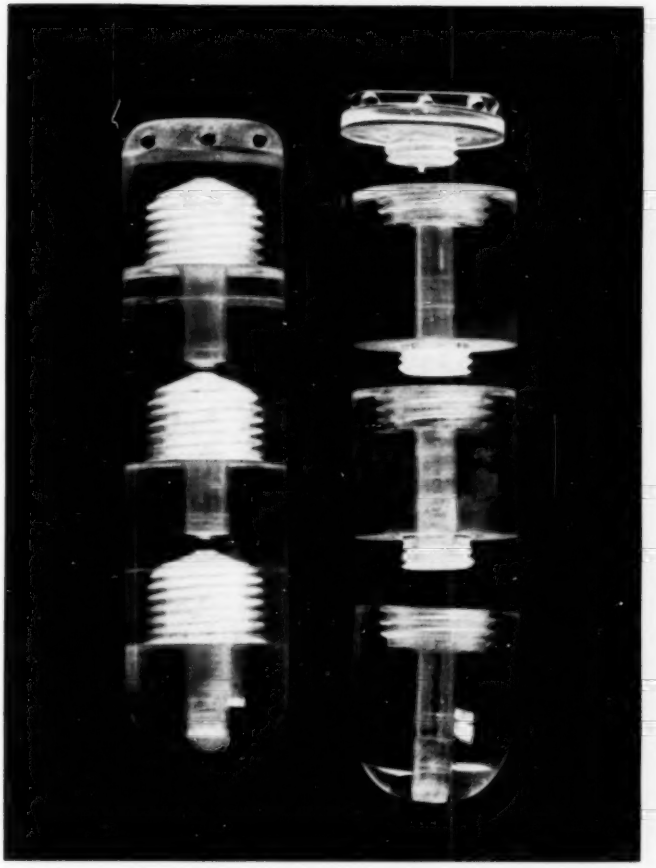

FIG. 1

Vaginal applicators of standard size. The screw mechanism of the examples shown are of different design.

A perspex cylinder is now used, made up of components 2.5 cm. long, each containing a source of radium. The length and diameter of the cylinder is chosen so as comfortably to fill the vagina, and it is kept in position by suturing the labia together. The usual size is 2.5 by 7.5 cm. Fig. 1 shows this applicator.

Originally a uniform surface dose of 8,000 r in 6 days was given, but this caused some rectal reactions and once a fistula, and the poor tolerance of the vulva to radiation was again demonstrated. A safe loading for the standard cylinder was found to be 15, 5, 10 mg. radium from above downwards for 100 hours. Fig. 2 is the isodose curves for this applicator.

Cylinders 2.0 and 3.0 cm. in diameter are used for vaginas narrower and wider than the average, loaded to give a similar dose rate on the surface; the length of the applicator is also modified when necessary for the individual vagina.

Results

Table I shows the results at 5 years, and the last column the number of vaginal recurrences observed to the present time, 5 to 15 years after the initial treatment.

Table II analyzes the vaginal recurrences observed, showing their site, time of appearance, and the course after treatment of the recurrence.

Table I

	No.	Lived 5 years	Well for 5 years without recurrence	Vaginal recurrence to present time
Hysterectomy only	64	57 (89.0)	50 (78.0)	7 (11.0)
Hysterectomy plus X-ray therapy	80	66 (82.5)	60 (75.0)	8 (10.0)
Hysterectomy plus vaginal radium	84	68 (81.0)	65 (77.0)	2 (2.4) (none in treated area)

Percentages in parentheses

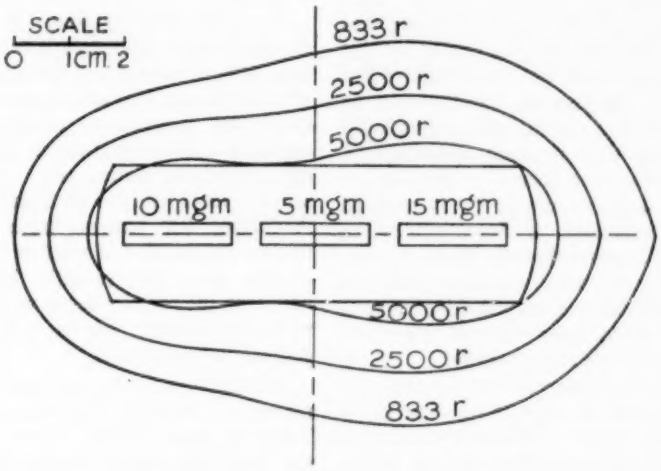

Fig. 2

Isodose curves for standard vaginal cylinder for 100 hours.

TABLE II

Vaginal Recurrences

	Site	Interval after hysterectomy	Treatment	Subsequent history
Hysterectomy only				
	Vault	4 months	Radium	Well 8 years
	Vault	4 years	Radium	Well 5 years
	Posterior wall	2 years	Diathermy	Well 6 years
	Multiple	5 years	Radium	Lived 2 years
	Vault	9 months	Radium	Well 7 years
	Vault	7 years	Radium	Well 2 years
	Vault	2 years	Radium	Lived 3 years
Hysterectomy and X-ray therapy				
	Vault	7 years	Radium	Lived 2 years
	Vault	4 years	Radium	Lived 1 year
	Right wall	4 years	Radium	Lived 5 years
	Anterior wall	3 years	Radium	Lived 2 years
	Vault	5 years	Radium	Lived 3 years
	Vault and urethra	1 year	Radium	Lived 1 year
	Urethra	15 months	Radium	Lived 1 year
	Vault	18 months	Radium	Lived 3 years
Hysterectomy and vaginal radium				
	Introitus	5 months	Radium	Lived 6 months
	Introitus	7 months	Radium	Well 6 years

DISCUSSION

It will be seen from Table I that the 5-year survival rate without recurrence of any kind was not significantly different in the three groups. As the vaginal recurrence rate was much higher in the first two, the reason for this is not clear. Since there were no fatalities due to either form of radiotherapy, and there are no plausible grounds for arguing that patients did less well because they received radiotherapy, the likeliest explanation seems to be that, on the whole, the less favourable cases received supplementary treatment. If this argument be accepted, it also appears that the X-ray therapy group, containing as many vaginal recurrences as the purely surgical one, may include patients whose disease would have recurred elsewhere in the pelvis but for the radiotherapy.

Thus, vaginal recurrence has so far occurred in some 10 per cent of patients not treated by vaginal radium after hysterectomy. Meigs (1929) examined 206 case histories and found that vaginal deposits were discovered in 13 (6.3 per cent) between 4 months and 5 years after operation. Rickford (1949) found 8 vaginal recurrences in 101 cases, within 5 years after hysterectomy, and suggested post-operative radium therapy to the vaginal vault.

The most striking result of the analysis is the observation that only 2 vaginal recurrences were seen in the radium series; as both of these were at the introitus and in patients whose vault alone was treated, the result achieved is the apparent entire prevention in this series of these deposits in the treated area. The work of the latest 5 years tends to confirm this observation. A further 100 patients have had the entire vagina irradiated, and the first recurrence in the treated area has recently been detected—a nodule in the anterior rectal wall. It is too early to know whether this is isolated, or one of generalized metastases.

Turning now to the treatment of the 17 recurrences, all of which were proved histologically, Table II gives details. Nine of them were in the vault only, and 1 woman had a deposit in the vault in addition to a sub-urethral metastasis. It has been suggested that recurrences

involving the vault scar are, sometimes at least, implants due to spill at operation, and support is lent to this theory by the fact that recurrences have sometimes occurred in the abdominal scar. Mere suture of the cervix is a dubiously efficacious preventive, and it might be found that preliminary radium therapy would reduce the incidence of this recurrence.

Several writers, latterly Way (1951), have drawn attention to the frequent appearance of a sub-urethral metastasis in carcinoma of the body of the uterus; of 14 vaginal deposits described by him, 13 were in this site, 9 being noticed at or before the diagnosis of the primary. The writer also has frequently observed this condition when the patient was first seen, or, occasionally, within a few weeks of hysterectomy; but it is noteworthy that the present series, consisting of patients well 3 months after hysterectomy, includes only 2 such cases, found 1 year and 15 months after hysterectomy. It seems that this peculiar metastasis does not tend to appear at a late stage after removal of the primary.

The frequently long latent period—4 years or more in 7 of the 17 cases—indicates the necessity for frequent examinations for many years if hysterectomy alone is used. This is seen to be the more important when it is observed that some of these recurrences can be cured; 5 of the series are well at least 5 years after treatment of the recurrence. Of the remainder, some died with the recurrence unhealed, others of distant metastases, and, in some instances, the information received indicates no more than death from cancer of the uterus. An accurate assessment of the frequency of multiple metastases is not possible.

Radium was used in every case, except one treated by diathermy in another centre. Intracavitary application was the rule, but the surviving case of recurrence at the introitus had a radium implant.

Summary

A series of 228 cases of adenocarcinoma of the body of the uterus, all apparently well 3 months after total abdominal hysterectomy, has been followed up for 5 to 15 years.

Of 64 treated by hysterectomy alone 7 (11 per cent) developed a vaginal recurrence; 8 (10 per cent) of 80 cases given X-ray therapy after hysterectomy. Of 84 in whom hysterectomy was followed by vaginal radium, 2 (2.4 per cent) recurred in the vagina, neither in the treated area.

The method of applying vaginal radium is described.

Nine of the recurrences were in the vaginal vault. Two only were sub-urethral. It seems that deposits in the latter site do not tend to appear long after removal of the primary. Four of the recurrences appeared later than the fifth anniversary of the hysterectomy.

Of the 17 cases having vaginal recurrence 5 were well 5 years later, and one is well after 2 years.

The 5-year survival rate without recurrence is the same in the three groups. A possible reason for this is offered.

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ANTEPARTUM FEMORAL THROMBOSIS

BY

CHARLES M. FLOOD, M.D., M.R.C.O.G.

Chief Assistant

Queen Charlotte's and Chelsea Hospitals, London

ANTENATAL thrombophlebitis is one of the rarer complications of pregnancy. A review of the subject by Donaldson (1950) has traced 49 reported cases of this condition, including 1 of his own, of which 7 occurred in the femoral, 3 in the iliac, and 3 in the caval veins. Estimations of its incidence must be inaccurate since, as Donaldson emphasizes, many cases are not reported. Westmann (1936) gives the incidence as 0.1 per cent while Browne (1946) records 3 cases in 12,000 booked cases at University College Hospital, an incidence of only 0.025 per cent.

Donaldson, in his report quoted above, states that he was unable to find any records of the use of anticoagulants in this condition. Since then, further cases of antepartum thrombophlebitis have been reported; 9 by Wright (1951), all treated with anticoagulants; 5 by Hallum and Newham (1951), none treated by anticoagulants before labour; 5 by Logan, O'Driscoll and O'Donoghue (1951), none treated by anticoagulants; and 1 fatal case by da Cunha (1952). Two further cases are here reported of antepartum femoral thrombosis in which anticoagulants were used without harm to mother or child.

Case 1

Mrs. Ann B., a primigravida of 33 years, was first seen on 29th January, 1948, when she was approximately 6 weeks pregnant, her last menstrual period having been 12th December, 1947. On general clinical and obstetrical examination, no abnormality was found. The heart was normal, the blood-pressure 110/60, with no albuminuria.

In 1932 and 1935 dilatation of the cervix had been performed for dysmenorrhoea. In 1945, dilatation and insufflation had been performed for sterility, and in 1946 curettage had been performed, following an incomplete abortion at 5 months. The Wassermann reaction was negative.

Antenatal progress was uneventful until 23rd July, 1948, when she was admitted at the urgent request of her family doctor with a diagnosis of acute cardiac failure. When seen at the antenatal clinic the previous week the uterus had been 32 weeks in size, L.O.A., the head not engaged, the foetal heart heard. The blood-pressure was 100/70. There was no albuminuria.

On admission she stated that she had been perfectly fit until she awoke at 3 a.m. on 23rd July, 1948, gasping for breath. She felt no pain but her "heart was fluttering". On sitting up in bed the dyspnoea and palpitations were partially relieved. In the morning she called her doctor, who arranged her admission to hospital.

Condition on examination. The temperature was 98.6°F., the pulse 136 per minute, the respirations 30 per minute. There was a systolic murmur at the apex with re-duplication of the first sound. The heart was not enlarged. The blood-pressure was 125/80. There was no oedema, no abnormality in the respiratory system, and no cyanosis. The thyroid was not enlarged. There was no abnormality in the central nervous system. The height of the fundus corresponded to 34 weeks, L.O.A. The vertex was fixed at the pelvic brim. The foetal heart was 140 per minute. There were no varicose veins and no evidence of saphenous, popliteal or femoral thrombosis. Homans' sign was negative bilaterally. The urine showed no abnormality. The portable chest X-ray showed no pulmonary or cardiac lesion. Electrocardiography was not available. The red blood corpuscles were 4,350,000, the haemoglobin 86 per cent, the white blood corpuscles, 7,500.

A diagnosis of sinus tachycardia was made and bed rest and sedation with phenobarbitone, gr. ½ thrice daily, and barbitone soluble, gr. 7½ h.s., were prescribed. By the following morning, 24th July, 1948, her pulse had fallen to 78 per minute and respirations to 22, and her condition improved during the next few days. On 28th July she complained of pain on the right side of the chest on inspiration, but, apart from a few crepitations at the right base, no abnormality was detected. The temperature was 98.4°F., pulse 100, and respirations 24. Two days later, 30th July, 1948, the pain at the right base on inspiration was worse, the temperature 98.4°F., pulse 100, and respirations 28. A pleural friction rub was now heard at the right base. There was no sign of thrombosis in the legs.

On 31st July, 1948, having passed a comfortable night, at 3.45 p.m., she felt a sudden severe " burning, knife-like pain " in the left leg, especially in the calf. The left leg was found to be grossly swollen throughout its entire length with maximal pitting oedema over the lower leg and foot. There was no tenderness except over the saphenous opening. Homans' sign was negative in both legs. The foetus was presenting in the L.O.A. position, the head now deeply engaged. The possibility of deep femoral thrombosis was considered but, in the absence of tenderness, raised temperature and a positive Homans' sign, was not seriously entertained.

The following morning, 1st August, 1948, the swelling of the leg was still greater, with tenderness now present along the course of the femoral vein and also deeply just above the inguinal ligament. The left calf was very tender, with a strongly positive Homans' sign. Vaginal examination revealed no intrapelvic abnormality. Accordingly, anticoagulant therapy was commenced by Dicoumarol, with loading doses of Heparin 10,000 units stat., followed by 5,000 units q.q.h. for 48 hours, and continued for 13 days, coagulation times and prothrombin times and indices being estimated daily. Dosage of Dicoumarol was adjusted daily to keep the prothrombin time in the region of 45 seconds and the prothrombin index between 20 and 25 per cent. She was kept in bed, but no general or local immobilization enforced, the bed-clothes merely being supported by a cradle over both legs.

On 5th August, 1948, after 5 days of anticoagulants, Mrs. B. felt very fit. The left leg had decreased in size, pain had diminished and active movements were further encouraged under the supervision of the physiotherapist.

On 12th August, 1948, she was allowed up. She had no pain in the leg on full active and passive movements, and there was no difference in the size of her two legs. She was discharged on 17th August, 1948.

Further antenatal progress was uneventful and she had a normal labour lasting 15 hours 20 minutes on 9th September, the day she was due. The third stage was normal and blood loss minimal, as was to be expected. The puerperium was uncomplicated, she was out of bed from her second day, and was discharged home on her 12th day with her baby, weighing 8 pounds 3 ounces.

Case 2

Mrs. Peggy D., a primigravida, aged 28, first attended the antenatal clinic in September 1949, the expected date of delivery being 27th April, 1950.

Apart from appendicitis when aged 10, jaundice when aged 4, and a dilatation of cervix, insufflation of tubes, curettage and correction of retroversion in May 1948, for infertility after 7 years of marriage, she had had no serious illnesses.

General examination revealed no abnormality in any system; the blood-pressure was 130/85 mm.Hg., and a non-catheter specimen of urine was normal.

She remained well until 13th March when, after walking downstairs, she experienced pain, of sudden onset, in the upper part of the chest. The pain, which was accompanied by dyspnoea, was of a constricting nature, but related neither to inspiration nor to expiration.

On admission to the ward her general condition was good, but she was obviously dyspnoeic at rest. The temperature was 98.4°F., the pulse rate 130, of good volume and normal tension, respirations 28. The blood-pressure was 130/80 mm.Hg. No pain was experienced on compressing the chest wall and no abnormal physical signs could be detected in the chest. Palpation of her abdomen showed the height of the fundus uteri to be equivalent to that of a 34-weeks pregnancy, the presentation being a breech with foetal heart heard. Slight tenderness, however, was elicited over the right femoral vein in the area of the femoral triangle.

A provisional diagnosis of pulmonary embolism secondary to femoral thrombosis was made although no definite pulmonary lesion could be demonstrated.

Treatment with Heparin was commenced and continued until the patient was fully ambulant 10 days later, on 23rd March, 1950. The pulse rate fell to 96 by the 3rd day, varying between 90 and 100 until the 8th day, then between 80 and 90 for a further week, thereafter being between 70 and 80.

Her symptoms subsided and she was discharged from hospital on 1st April, 1950. At this time she was approximately 37 weeks pregnant, the presentation now being a vertex (spontaneous version having taken place soon after admission to hospital), the blood-pressure was 130/80, and urine albumin-free.

On 13th April the patient was readmitted in labour. Her general condition was good and there was no evidence of deep thrombosis. After a short labour lasting 5 hours 20 minutes she was delivered normally at 6.50 a.m. of a female child whose birth weight was 6 pounds 5 ounces. The blood loss was normal in amount and a second degree perineal tear was repaired with catgut and silkworm gut sutures.

The puerperium remained normal until the 7th day, 20th April, when she complained of some discomfort in the right leg. On examination there was tenderness to deep pressure in the midline over the calf muscles and Homans' sign was positive. Her temperature showed small peaks of elevation to 99°F., the pulse rate being between 80 and 90.

Heparin therapy was immediately recommenced and the patient, previously ambulant, was now confined to bed with no restriction on movement in bed.

On 23rd April she complained of sudden pain in the left chest. This was accompanied by cyanosis and a moderate degree of dyspnoea. Her temperature was 100°F., pulse rate 124, and respiration 30. No abnormal physical signs could be detected in the chest, but pain was apparent on deep inspiration. Penicillin was now given in addition to Heparin.

During the afternoon of 25th April she experienced 3 further attacks, each being accompanied by dyspnoea and mild cyanosis. At 11 p.m. a fourth attack was accompanied by marked cyanosis and dyspnoea. Respirations were 32, pulse rate 120, and temperature 101°F. The quantity of Heparin was increased, morphine sulphate gr. 1/6 was administered subcutaneously, and the patient placed in an oxygen tent. No further attacks took place but by the 28th the patient still showed a tendency to cyanosis on being removed from the oxygen tent.

A skiagram of the chest on 25th April revealed no conclusive evidence of a pulmonary embolus.

By 1st May her condition had improved and the oxygen tent was no longer employed. Examination of the chest showed signs of residual fluid at the left base. The Heparin (now given as Heparin Retard) was reduced to a bi-daily dose and the patient was allowed out of bed.

By 7th May her condition was much improved and she was now ambulant. Heparin therapy was discontinued on 8th May and the patient was discharged on the 11th, having completely recovered.

Subsequently, 2 weeks after discharge, she developed a deep thrombosis of the left leg which was treated at home by rest and crêpe bandaging.

On examination at the postnatal clinic 6 weeks after birth no abnormality could be detected in either leg.

Discussion

Both these cases occurred in young primigravidae, though Browne (1946) states that 70 per cent of cases occur in multiparae. Logan *et al.* (1951) likewise emphasize multiparity as an aetiological factor. In their 5 cases the parity ranged from 3 to 11, with the presence of anaemia and septic foci as important accessory factors. Neither of the two cases here reported had any previous history of cardiovascular disease, or varicose veins, though both had undergone a minor gynaecological operation at least once. Both occurred between 30 and 34 weeks. Both had the same initial symptoms of dyspnoea and palpitations, the one when asleep in bed and the other while walking downstairs. The exact sequence of events in Case 1 is by no means clear. Presumably a silent thrombosis of the femoral or iliac vein occurred, giving rise to a pulmonary embolus which caused her initial symptoms on 23rd July, 1948. Either this thrombosis was insufficient to cause symptoms and signs in the leg or a fresh thrombosis occurred on 31st July, when the diagnosis became obvious, though if no further thrombosis occurred then the long latent period from 23rd July, or before, until 31st July is unusual.

In their review of 108 cases of pulmonary embolism in 1945, Sagall, Bornstein and Wolff found that the condition simulated pneumonia, angina pectoris, myocardial infarction, pleurisy, vascular collapse or acute heart failure in a large proportion of cases.

The subsequent courses of these 2 cases differ considerably.

Case 1, who was treated with Heparin and Dicoumarol, with daily estimations of prothrombin time and indices, was apyrexial throughout, had no relapses, carried to term, and had a normal puerperium. Case 2, who was treated with Heparin both in its normal intravenous and depot form, had no daily controls and on more than one occasion in her notes is the remark that clinically she did not appear to be adequately heparinized. This would seem to be substantiated by her subsequent course which was pyrexial, with premature labour at 38 weeks and a severe relapse during the puerperium.

It is impossible to draw conclusions from 2 cases, but the lack of sufficient laboratory control in the second case must have had a detrimental effect. It is of interest that the coagulation time and prothrombin time prior to heparinization in Case 1 were normal, as was found by Steiner (1945).

da Cunha (1952) reports the case of a woman of 40 years, with 5 previous normal confinements, who developed pulmonary embolism and bilateral femoral thrombosis 2 weeks after she first developed a unilateral deep femoral thrombosis. After 24 hours treatment with Heparin she developed a haematoma of the rectus muscle and at laparotomy she died. Postmortem confirmed the presence of the underlying pulmonary embolus and bilateral femoral thrombosis. However, it is felt that this isolated case, in which Heparin therapy was commenced 2 weeks after the femoral thrombosis was first manifest and only when the patient was already gravely ill, should not adversely influence the early and adequate use of anticoagulant therapy in cases of antenatal thrombosis. Moreover, Hallum and Newham (1951), who gave anticoagulant therapy to only 1 of their 5 cases and then only when the condition had been established for 19

days, emphasize the serious morbidity from this condition when treated conservatively. This view is further supported by Logan *et al.* (1951). Donaldson (1950) alludes to the danger of allowing the patient to come into labour " without her full natural powers of arresting haemorrhage." In these 2 cases, anticoagulant therapy stopped several weeks before labour, so that no conclusions can be drawn. However, since the arrest of uterine haemorrhage is primarily dependent on the efficiency of uterine retraction, it is felt that in any case the theoretical dangers from postpartum haemorrhage are less than those actually arising from inadequately treated thrombosis, as is clearly shown by Case 2.

Summary

Two further cases of antepartum femoral thrombosis are recorded, both occurring between the 30th and the 34th weeks of pregnancy in young primigravidae.

Both cases presented as acute cardiac or pulmonary emergencies without any previous precipitating factor.

Both were treated with anticoagulants, the one with adequate pathological control, the other without. The difference in their progress was most marked, though both eventually recovered fully.

Both pregnancies continued, the one to term and the other to the 38th week. Labour in each case was normal with no undue loss in the third stage as was to be expected.

The value of adequate anticoagulant therapy is stressed as opposed to the theoretical dangers of postpartum haemorrhage, and the decided morbidity from conservatively treated antepartum thrombophlebitis.

I wish to thank Mr. W. Netley Searle and Mr. W. R. Winterton for their advice and permission to publish these records of their patients.

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SOME OBSERVATIONS ON THE TREATMENT OF ECLAMPSIA WITH SODIUM THIOPENTONE

BY

DR. M. K. KRISHNA MENON, B.A., M.D.

Professor of Clinical Obstetrics and Gynaecology
Madras Medical College, Madras

Obstetrician and Gynaecologist
Government Hospital for Women and Children, Madras, India

ONE thousand one hundred and fifty cases of eclampsia were treated in this hospital during the years 1938–50. The maternal mortality varied from 9 per cent in some years to as high as 20 per cent in certain other years—the average being 15.1 per cent. Eclampsia is notorious for its varying mortality. So long as the cause of eclampsia remains unknown so long will the treatment be symptomatic and uncertain. We have during the last 12 years given the conservative treatment of eclampsia a thoroughly extended trial using various sedatives, alone and in combination with artificial rupture of membranes, and we have realized that we are unable to reduce our maternal mortality below 12 per cent on an average. It was therefore with great hopes that I started to try out the Sodium Thiopentone Dextrose therapy advocated by Professor O'Donel Browne (1950). All cases of eclampsia admitted into the hospital from 1st October, 1951, were treated on the lines given below. Seventy-five cases were treated till May 1952, when I stopped the treatment. The cases treated were consecutive ones and no selection of cases was made.

The Treatment Adopted

It is almost exactly the same as given in Professor Browne's paper. On admission a rapid examination is first made with the minimum of disturbance to the patient, who is kept in a special ward for eclamptics only. The patient is then given intravenously 0.5 g. of pentothal sodium in 20 ml. of distilled water slowly as an induction anaesthesia. (Abbott's pentothal sodium has been used throughout.) As soon as the patient is under the effect of pentothal, a continuous drip containing 3 g. of pentothal sodium in 1,000 ml. of 20 per cent dextrose is set up. This intravenous drip is allowed to flow in at the rate of 15 to 20 drops a minute depending upon the condition of and its effects on the patient. If the patient is very restless, from a syringe containing 0.5 g. of pentothal in 20 ml. of distilled water, 2 ml. are injected into the rubber tubing and this is repeated till the patient is absolutely quiet and is soundly asleep. Oxygen is administered right from the start at the rate of 3½ litres per minute and an airway is put in soon after induction. A rubber catheter is put in the bladder which is kept continuously drained. The pulse, respiration, blood-pressure and urinary output are recorded every hour. A medical officer stays with the patient day and night watching her carefully, allaying restlessness by injections of pentothal from the syringe and adjusting the rate of the drip. Individuals vary considerably in their response to pentothal. While in some small doses give marked sedative effect, in some much larger doses are necessary. Hence it is impossible to standardize the treatment and individual attention is very necessary. I have not continued the pentothal drip in any case for longer than 24 hours and no patient had more than 1½ litres of the 20 per cent dextrose in 24 hours. When the patient is well under the influence of pentothal and has been quiet for about 24 hours, the pentothal drip is replaced by 20 per cent dextrose solution and this is continued for another 24 to 48 hours—the duration depending upon the urinary output, the response to treatment and the presence or absence of pulmonary complications. Not more than 1½ litres are given in 24 hours. The patient

is put on prophylactic penicillin injections. To accelerate the progress of labour the membranes are artificially ruptured as soon as labour pains start and the cervix is effaced. The second stage is cut short by forceps or breech extraction as soon as conditions for easy delivery are obtained. No anaesthesia is given for completing the delivery in these cases except in some cases to give an extra 0.1–0.2 g. of pentothal through the syringe. The throat of the patient is kept clear of all mucus. The patients are constantly watched for pulmonary oedema and cardiac complications. Once the acute phase is over and the patient has got over the eclampsia—and most of the cases by now would have delivered—she is put on light liquid nourishments to start with and the diet gradually increased. For bowel action concentrated magnesium sulphate is given by mouth, once consciousness has returned.

Effects on Respiration

Pentothal is a respiratory depressant. Except in 2 cases, where the respiratory rate fell to 10 and 12 per minute for a short while, in all others it was over 20 per minute. The average for all cases was 30 per minute. In the fatal cases, the respiratory rate was high right from the start of induction with pentothal and the average for all the fatal cases was 42 per minute. In the cases that survived the rate was 28 per minute. One case in the series died of sudden respiratory failure after the pentothal drip had been going on for a few hours. The failure was a sudden one and the patient could not be revived. With oxygen being administered right from the start, an airway put in soon after induction and the throat kept clear of mucus one need not be anxious about respiratory failure in these cases. But all the same, a very careful watch has to be kept. A very rapid rate during treatment—40 or over—seems to me to be associated with a bad prognosis (Table I).

The Pulse

In all cases soon after induction the pulse rate showed a tendency to increase. On an average, the pulse rate was 130 per minute, of good volume and regular during the whole period of administration of pentothal. In the fatal cases, however, a tendency for a very rapid pulse was markedly noticeable. The average pulse rate for the fatal cases during the period the patient was under pentothal was 146 per minute (Table I). As mentioned previously, all the fatal cases were also associated with a very rapid respiratory rate —42 on an average per minute. Ninety per cent of cases showing an average pulse rate of 146 and respiratory rate of 42 and over during treatment died. It is quite possible that this is the result of acute myocardial damage due to eclampsia; but whether pentothal had any hand in accelerating or enhancing the damage I am not in a position to say. Having constantly watched these cases, I can give it only as my impression that pentothal cannot be completely exonerated from blame in the production of this

TABLE I

No.	Amount of pentothal given (g.)	Duration of administration (hours)	Average respiratory rate per minute	Average pulse rate per minute	Remarks
1.	4.7	21	46	148	Died
2.	3.85	17	44	148	Died
3.	1.765	7	46	150	Died
4.	2.7	Interrupted	44	148	Died
5.	2.05	11	48	150	Died
6.	1.325	4½	30	130	Died of sudden respiratory failure
7.	3.5	21	46	146	Died
8.	1.25	8	44	144	Died
9.	3.15	13	44	146	Died
10.	3.55	14	50	150	Died
11.	3.2	10	42	146	Died
12.	1.125	6	44	146	Died

clinical phenomenon which invariably ended fatally in spite of cardiac stimulants being used during the administration of pentothal.

The Blood-pressure

No significant fall in blood-pressure occurred in general during the pentothal therapy. In 80 per cent a significant fall was observed only 24 to 48 hours after delivery. But one thing was noticeable—in 60 per cent of the fatal cases there was a tendency for a fall in blood-pressure along with an increasing pulse rate and respiratory rate even during the administration of pentothal. It seems to me that a rising pulse and respiratory rate along with a falling blood-pressure during pentothal therapy are signs of bad prognosis. I was so convinced of it that in my later series of cases, where this particular phenomenon was observed, I discontinued the therapy even at the risk of recurrence of fits. The sequence of events can only be explained as manifestations of acute myocardial failure.

The Urinary Output

Sixty per cent of cases had a good urinary output, i.e., over 600 ml. in 24 hours. In 30 per cent the output was between 300 ml. and 400 ml. while in 10 per cent it was less than 200 ml. in 24 hours. The last group was almost always fatal. Ten cases developed frank haematuria while under pentothal therapy. Microscopically the urine contained plenty of red blood cells and a few leucocytes. It worried us a lot. Was the haematuria due to pentothal or was it an early manifestation of renal damage in eclampsia? In 4 cases I stopped the pentothal treatment when the haematuria was noticed. One of them died. In 6 cases in which I continued with the pentothal 2 died and in the rest the urine cleared up even during the treatment with pentothal. In those cases where the pentothal was stopped because of the haematuria, the urine cleared up within 6 to 8 hours. It is possible that haematuria is really a symptom of renal complications setting in during eclampsia and not due to pentothal (Table II). In 1 of the fatal cases who developed haematuria a partial postmortem was obtained and the kidneys showed typical symmetrical cortical necrosis. It is evident that haematuria is a symptom of bad prognosis.

The Fits

So far, in the very large number of eclamptics treated in this hospital, whatever the sedatives we have used, fits have recurred in 47 per cent of cases. Since the institution of the pentothal therapy a very marked improvement in the recurrence rate was noticed. I am now convinced, after observing a very large number of cases using different sedatives, that for stopping the convulsions and preventing their recurrence intravenous pentothal drip therapy is perhaps the best method. During the administration of the drip 40 per cent of cases showed restlessness and twitching of the muscles of the upper and lower extremities. Perhaps these would have developed into renal convulsions had not the attending doctor immediately controlled this

TABLE II

No.	Amount of pentothal given before haematuria set in (g.)	Whether pentothal stopped or continued	Time of clearing up of haematuria	Result to mother
1.	2.65	Stopped	6 hours after stopping	Alive
2.	1.50	Stopped	5 hours after stopping	Alive
3.	1.3	Stopped	6 hours after stopping	Alive
4.	1.85	Continued	10 hours after onset	Alive
5.	1.9	Continued	Did not clear	Died
6.	2.05	Continued	8 hours after onset	Alive
7.	1.0	Continued	10 hours after onset	Alive
8.	2.4	Continued	Did not clear	Died
9.	1.00	Stopped	Did not clear	Died
10.	2.15	Continued	10 hours after onset	Alive

easily by injecting 2 ml. of pentothal contained in the syringe. So long as we can keep the patient quiet and asleep by injecting if necessary the minimum quantity of pentothal while the drip is flowing, I feel there is no danger of the fits recurring. In this series 7 cases had recurrence of fits—i.e., 9.5 per cent. Two were very early cases where pentothal was stopped prematurely while we were feeling our way with regard to the dosage. In 2 cases pentothal was discontinued prematurely owing to haematuria and in 3 due to acute myocardial failure. I am fully convinced that one need have no anxiety regarding the recurrence of fits when the patient is on this line of treatment so long as the dosage is sufficient and the pentothal not prematurely discontinued.

The Dosage

No hard and fast rule can be laid down regarding the dosage. Each case has to be assessed carefully during the treatment and the rate of flow of the drip and the total quantity given adjusted according to the reaction and response to treatment. Patients vary much in their response to the drug. It is also possible that the severity of the eclampsia plays perhaps a greater role in this varying response. I have not given to any patient more than 5 g. in 24 hours. From watching these patients constantly I have come to realize that pentothal is not so very harmless to the eclamptic. I have lost too many of these eclamptics treated by this method for no obvious cause other than acute cardiac failure setting in during treatment.

The Recovery

Here again patients react differently in the time required to regain full consciousness after pentothal treatment. I have found that with an average dose of 3 g. in 18 hours a patient takes about 6 to 8 hours to recover almost full consciousness. In some cases with smaller doses recovery has taken 10 to 12 hours and in 3 of the fatal cases the patient never recovered consciousness, even though the amount given was only between 2.5 and 3 g. Mental confusion after recovery was a distressing symptom in 5 per cent of cases. One of the patients developed acute mania and died. In the rest the disorientation and confusion persisted on an average for 96 hours before they recovered fully.

The Labour

The management of labour in eclampsia has in this hospital been always conservative. Since 1938 we have adopted artificial rupture of membranes to accelerate labour and to induce premature labour in eclamptics as an adjuvant to the sedative line of treatment, irrespective of the nature of the cervix, except of course in those cases with cephalo-pelvic disproportion, or other complications pointing to Caesarean section. The only active interference was in the nature of helping out a head on the perineum with forceps or breech extraction to cut short the second stage of labour. This attitude had been maintained largely in this series also. But on careful observation of a large series of cases I was getting more and more convinced that the sooner the uterus is emptied in eclampsia the better it is for the patient. Gradually I started to pick up a few cases of antepartum eclampsia and deliver them by Caesarean section, as soon as they were under the influence of pentothal. Five cases were treated on this line. All were primigravidae with unengaged head and uneffaced cervix and not in labour. One case died. This was one where the Caesarean section was done in a patient who was in a very low condition with concealed accidental haemorrhage. The other 4 made a marvellously quick recovery. All sections were done under pentothal and local infiltration anaesthesia. All were lower segment Caesarean sections. All of us have witnessed the dramatic recovery a patient makes on emptying the uterus in severe pre-eclampsia. If that be so why should we not do the same in eclampsia? Caesarean section in eclampsia fell into disrepute because of the high maternal mortality. But then those were the days when lower segment Caesarean was still in its infancy, anaesthesia was not well developed and antibiotics were unknown. Now under modern conditions with all its advantages is it not time that we revised our attitude towards Caesarean section in eclampsia? Would it not be the better line of treatment to resort to in a primigravida with antepartum eclampsia, round about term, with

an uneffaced cervix and an unengaged head? If we are convinced that emptying the uterus does help—and I am convinced it does—I see no reason why Caesarean section should not be done in eclamptics as soon as they are under the influence of sedatives. It is necessary, however, that if this procedure is to give good results it must be done early enough and not as a last resort when all methods have failed to control the fits. Only local anaesthesia should be used and lower segment operation should be preferred.

Maternal Mortality

Twelve patients died out of the 75 cases treated by this method—mortality rate 16 per cent.

Cause of Death

Respiratory failure	1
Pulmonary oedema	2
Cerebral haemorrhage	1
Post-operative shock	1
Cortical necrosis of kidney	1
Acute cardiac failure	6

The inference is obvious. While pentothal may perhaps be the best drug in the control of convulsions, in my series of cases it has not helped in any way to bring down the maternal mortality.

Infant Mortality

Out of 59 cases who delivered, 22 babies were born dead—a foetal loss of 40 per cent. It is difficult to assess the effect of pentothal on the foetus. Of the babies born alive 60 per cent were asphyxiated but could be revived without difficulty. How much of it is due to the eclamptic state and how much to pentothal it is difficult to assess.

I must mention here what a strain it is to the medical staff undertaking this line of treatment. The constant careful attention which is the essence of this method gives a very anxious time to the doctor and I am constrained to admit that from my experience the results obtained have not been commensurate with the stress and strain gone through.

Summary and Conclusions

Seventy-five cases of eclampsia treated during a 7-month period from October 1951 to May 1952 by the Sodium Thiopentone Dextrose therapy advocated by Professor O'Donel Browne are reported.

Details of treatment are given along with some special observations during the administration of pentothal.

The maternal mortality in the series was 16 per cent. Pentothal, which perhaps is the best drug for the control of fits, has not helped to reduce the maternal mortality.

From 1938 to 1950, 1,150 cases of eclampsia were treated on conservative lines with a mortality of 15.1 per cent. It is felt that conservative treatment cannot improve the maternal mortality further. A suggestion is put forth that sedation and early Caesarean section—lower segment section under local anaesthesia—may help to reduce the maternal mortality. It is proposed to try out a series of cases on these lines and report at a later date.

It is a pleasure to acknowledge my gratitude to all the medical officers who helped me in this work. But for their untiring efforts and enthusiasm and the hour-to-hour detailed notes on each case they made, this work could not have been carried out and published. I am very grateful to them and to the Superintendent, Dr. Tampan, for affording me full facilities to carry out this work.

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VARIATIONS IN THE HISTOLOGICAL APPEARANCES OF THE ASYMPTOMATIC POST-MENOPAUSAL ENDOMETRIUM

BY

VYVYAN DAVIES, M.D., F.R.C.S.E.

AND

GEOFFREY F. WILLIAMS, M.B., M.R.C.O.G.

Department of Obstetrics and Gynaecology, Morriston Hospital, Swansea

THE histology of the cyclical changes which the endometrium undergoes in response to hormonal stimulation during reproductive life is well known, adequately described, and pictured in the standard English textbooks on gynaecology. The histological appearance of the post-menopausal endometrium, however, appears to have been given comparatively little attention or description in these textbooks. It is natural to anticipate that the endometrium, after the menopause, will partake in the normal involutionary and atrophic changes exhibited by the rest of the organs of the generative tract at this period of life. It is well recognized, however, that the post-menopausal endometrium is capable of being activated by oestrogens, either derived from ovarian or extra-ovarian sources, or administered therapeutically. Our interest in the histology of the asymptomatic post-menopausal endometrium was stimulated by the following case, which paradoxically had bleeding in the form of "spotting" as the presenting symptom.

Mrs. C. W. G., aged 62 years, was seen on 17th August, 1951. She was a para-2, and her last pregnancy was 23 years ago. She had the menarche at 12 years of age, and menstruated regularly 5/28, until the age of 57 years, when she stopped suddenly. She had noticed slight "spotting" on 3 consecutive days during the week preceding this consultation. She had had no previous serious illnesses apart from mastoiditis when 23 years of age. She said her weight was stationary, and she had never taken any "oestrin" preparations at any time.

On examination she had a healthy appearance, and was of spare build. Her cardiovascular system was normal, and her blood-pressure 138/74 mm.Hg.

Abdominal examination revealed no abnormal lumps or tenderness.

On speculum examination her cervix and vagina presented a normal appearance.

Bimanually, the uterus was normal in size for her age, and also in shape, position and mobility, and no adnexal pathology was detected. On 27th August an examination was carried out under general anaesthesia, and the above findings were confirmed. The cervix was dilated up to No. 12 Hegar, and an empty sponge-holding forceps was inserted into the uterine cavity, and twisted round after opening and closing its jaws. The tissue removed came away in one piece, and in its triangular shape and its size it resembled a cast of the uterine cavity. No further material was subsequently removed with a curette. The thickness of the cast varied from 9 mm. in its upper part to 3 mm. in the lower portion. Its length was 5.5 cm. Its breadth was 4 cm.

The pathological report was as follows:

"The uterine cast consists of endometrial polypoid tissue with much cystic formation and rather fibroid stroma. The endometrial epithelium is proliferative in type, indicating activity of oestrogen. I can find no malignant features in it."

Figs. 1 to 4 show the macroscopic and microscopic appearance of this specimen.

The patient has been seen again on 3 subsequent occasions. She has had no further bleeding, and the pelvic findings still remain the same.

"Spotting," in common with all other degrees of post-menopausal bleeding, must be regarded as a symptom of sinister importance until proved to be otherwise by prompt investigation. The appearance of the endometrium in this case certainly suggested oestrogen stimulation, comparable to that seen in metropathia haemorrhagica of reproductive life. No source of this apparent continued stimulation has subsequently been found in this case.

In order to ascertain the variations in the histology which may be expected in the asymptomatic post-menopausal endometrium, we undertook a survey of the histology of the endometrium obtained from 40 cases dealt with in the last 3 years. The uterus in these cases had been removed vaginally as part of the operation for complete procidentia.

Surveys of cases in the past have suffered the drawback of either presenting symptoms of bleeding, or of being too near the menopause for the author to be dogmatic in stating that the endometrium was in fact truly post-menopausal. We have, therefore, only included for the purpose of this review:

(*a*) those cases in which the procidentia was not accompanied by genital haemorrhage, and

(*b*) cases that were 5 or more years post-menopausal, while we have carefully excluded all cases where oestrogen therapy had been administered.

The ages of the patients ranged from 54 to 73 years, and the period since the menopause was from 6 to 26 years. The microscopic picture of the cases in our series fell broadly into the 4 categories described by Novak and Richardson (1941).

(1) Atrophic type: 16 cases (40 per cent). Figs. 5 and 6.

(2) Proliferative type similar to the follicular stage of the normal cycle: 2 cases (5 per cent). Fig. 9.

(3) Active hyperplasia with "Swiss cheese" pattern: 10 cases (25 per cent). Fig. 7.

(4) Retrogressive hyperplasia with "Swiss cheese" pattern: 12 cases (30 per cent). Fig. 8.

Two cases of endometrial polypi were found in our series, and both showed endometrium of the active hyperplastic "Swiss cheese" pattern, both in the polyp itself and in the lining of the rest of the uterus.

Commentary

Speert (1949) recorded a series of 60 similar cases, 2–35 years post-menopausal, in which the endometrium was obtained by vaginal hysterectomy during operation for procidentia. In 72 per cent of this series the endometrium showed cystic dilated glands, in the remainder the endometrium was atrophic. Three cases only of Type 3 were found, and in 2 of these cases oestrogenic therapy had been administered, and in the remaining case there was a strong possibility of a co-existing ovarian tumour.

Novak and Richardson (1941) reviewed the post-menopausal endometrium in 137 cases, but 59 of these exhibited bleeding. These authors concluded that the post-menopausal endometrium could be described as falling into the 4 main types as stated above. This series is not strictly comparable with ours, or with that of Speert, inasmuch as in many of their cases specimens were obtained by curettage only and, as previously stated, 59 cases were examined because of the symptom of bleeding. We deduced from this series that of their 78 asymptomatic endometria, 33 (42 per cent) fell into the atrophic Type 1; 4 (5 per cent) into Type 2; 16 (21 per cent) into Type 3; and 25 (32 per cent) into Type 4.

It is difficult to understand how Speert was unable to find any cases of Type 4. It is easy to understand that no case of Type 2 was seen, as this appears to be a rare type, and comprised only 4 cases in Novak and Richardson's 78 asymptomatic cases. It would appear to us, from a study of Speert's publication and his photomicrographs, that a certain proportion of his endometria fall into Type 4. Only in this way can these two series be reconciled. Granted this assumption it will be seen that our series is in contrast to Speert in that Type 3 is a relatively common category, whereas, as stated previously, Speert could only find 3 cases, and these could be explained by extraneous oestrogen stimulation.

From our admittedly smaller number of cases, we can confirm what can be deduced from Novak and Richardson's series, namely, that all 4 types may be found in the asymptomatic post-menopausal endometrium; that the typical atrophic type is only found in approximately 40–50 per cent of cases, and that in about a third of the cases the endometrium will show the histological characteristics of Types 2 and 3, types which, in the endometrium of reproductive life, are associated with oestrogenic stimulation.

FIG. 1

Endometrial cast. Patient aged 62, 5 years post-menopausal. Scale in centimetres.

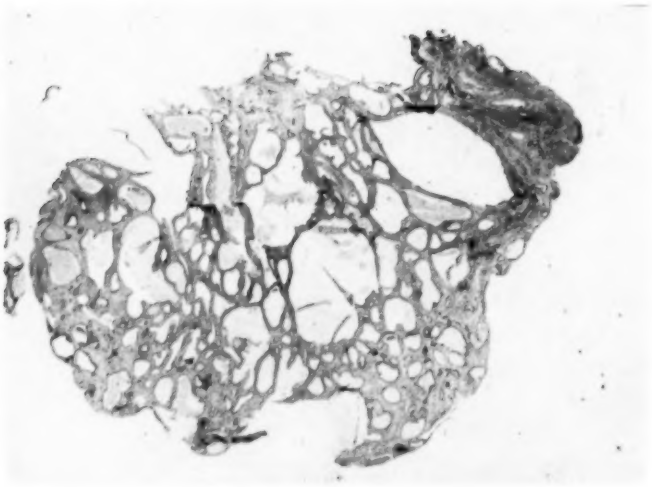

FIG. 2
Section of part of endometrial cast showing cystic hyperplasia. ×9

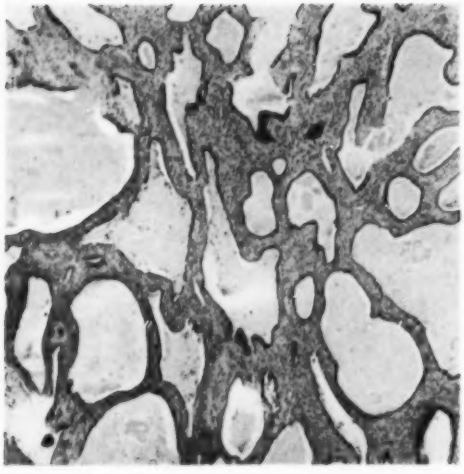

FIG. 3
Section of endometrial cast. ×43

FIG. 4
Section of endometrial cast showing active lining to the glands and the inactive stroma cells. ×360

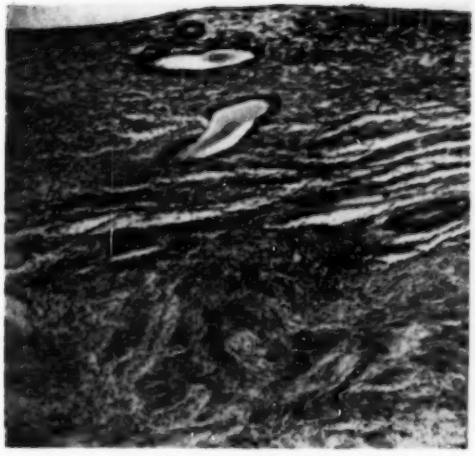

FIG. 5

Section of endometrium. Atrophic Type 1. Patient aged 64, 10 years post-menopausal. ×90

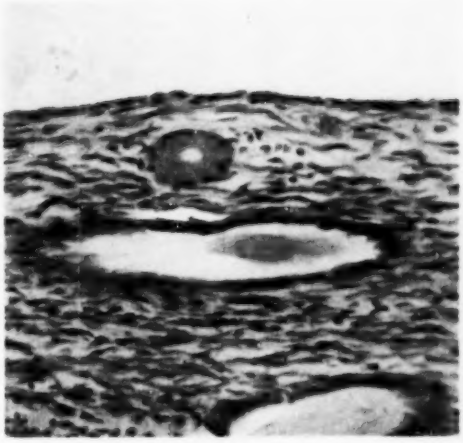

FIG. 6

Higher-power photomicrograph of Fig. 5 showing the hyalinization and fibrosis of the stroma. ×360

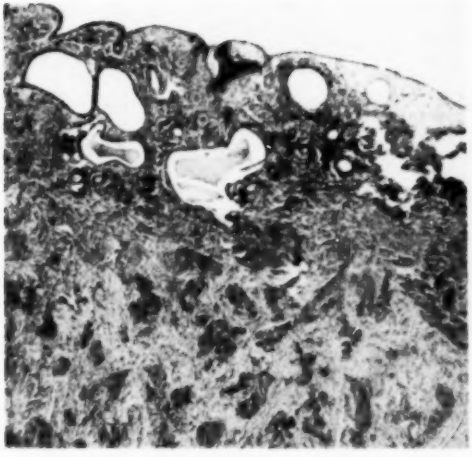

FIG. 7

Section of endometrium showing the active hyperplasia "Swiss cheese" Type 3. Patient aged 62, 16 years post-menopausal. ×45

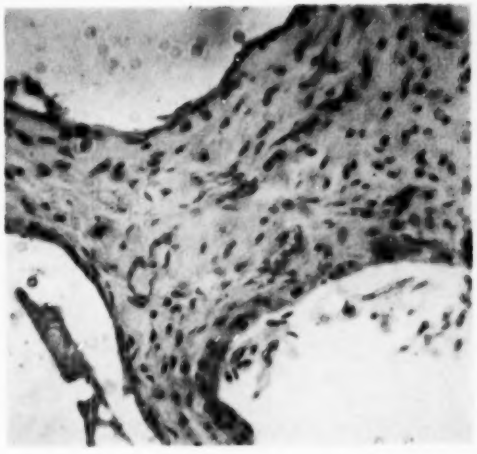

FIG. 8

Section of endometrium showing retrogressive hyperplasia "Swiss cheese" Type 4. Patient aged 66, 19 years post-menopausal. ×360

FIG. 9
Section showing proliferative Type 2 endometrium. Compare with Fig. 5 which is a higher magnification. Patient aged 54, 7 years post-menopausal. ×45

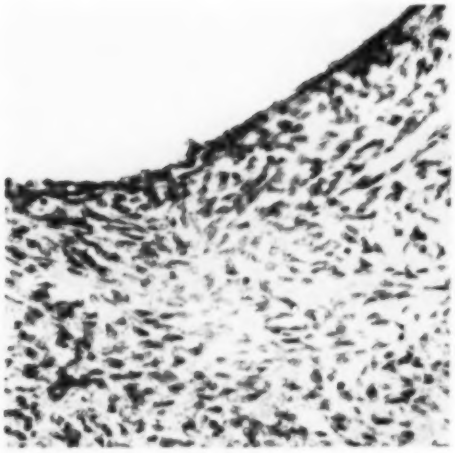

FIG. 10
Section of endometrium showing active hyperplasia of the stromal cells and an inactive gland lining. Patient aged 60, 9 years post-menopausal. ×360

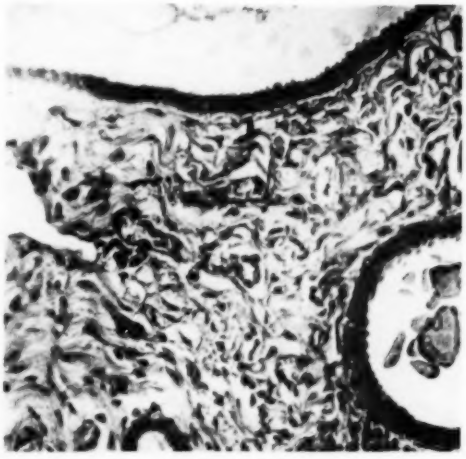

FIG. 11
Section of endometrium showing active gland cells and an inactive stroma. Patient aged 56, 10 years post-menopausal. ×360

From the examination of our slides we are in agreement with Novak and Richardson that there are cases where there is a transition from the active hyperplasia of Type 3, to the retrogressive hyperplasia of Type 4. Some sections show a markedly active stroma with an inactive lining to the glands, whereas others show an active gland lining with a hyalinized and fibrotic stroma (Figs. 10 and 11). These cases, however, are few in number—3 cases only—and, to avoid making a further type, have been classified with the group to which they appear to have the closest affinity.

The degree of vascularity in all our sections appears to bear no relationship to the type of endometrium present. Small vessels are found in all the types, many lying as stated by Speert in the sub-epithelial surface layer. It is quite likely that, as he postulates, rupture of one of the cystic glands tears the over-lying thin-walled vessel and so gives rise to bleeding.

Despite the fact that Types 2 and 3 strongly suggest endometrial activity, this should not necessarily lead us to infer a pathological cause, as Type 2 endometrial activity can be stimulated by oestrogen therapy, and Type 3 occurs in a quarter of asymptomatic post-menopausal endometria.

Summary

(1) A case resembling a complete endometrial cast in a patient 62 years of age, and 5 years post-menopausal, is described.

(2) A review of the histological appearance of the asymptomatic post-menopausal endometrium in 40 cases has been presented.

(3) These endometria fall into 4 main types.

(4) Active endometrial activity was found in a third of the cases.

We wish to express our thanks to Professor G. I. Strachan, Welsh National School of Medicine, and to Dr. A. F. Sladden, Pathologist, Glantawe Hospitals Group, for their constructive criticism and encouragement; and to the Institute of Pathology, Cardiff Royal Infirmary, for their help in the preparation of the photomicrographs.

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RELIEF OF PAIN AFTER EPISIOTOMY

Clinical Trial of Efocaine

BY

W. A. W. DUTTON, M.B., M.R.C.S., D.Obst.R.C.O.G.

Formerly Obstetric House Surgeon, St. Mary's Hospitals, Manchester

SOME degree of local perineal pain is very common after episiotomy. Sometimes the pain is so severe that the puerperium is made extremely trying for the patient.

There have been two main approaches to this problem in the past. The first method consists of some form of episiorrhaphy, either by the use of special fine sutures (Morse, 1946) or by employing an intracutaneous knotless suture (Rucker, 1939). This method is not uniformly successful. The second method utilizes the prolonged local anaesthetic effect of anaesthesic-oil solutions (Hunter, 1939; Shefferym, 1940). However, this method has become *démodé* because of the dangers of local abscess formation due to the irritant nature of the substances employed.

A new product is now available, marketed under the name of Efocaine, composed of procaine base, 1 per cent, with procaine hydrochloride, 0.25 per cent, and butyl.p.amino-benzoate, 5 per cent, in propylene glycol, 78 per cent, and polyethylene glycol 300, 2 per cent. This solution is saturated, but on contact with body fluids the local anaesthetic is immediately precipitated in a relatively insoluble form. These drug depots are then slowly absorbed to elaborate the anaesthetic action over a prolonged period (Ansbro *et al.*, 1952).

Clinical Trial

In this study the therapeutic possibilities of Efocaine were observed in a series of 20 patients.

The technique of episiotomy and the subsequent repair was the same in all cases. A right medio-lateral incision was used, the length varying with the requirements of the case. Dettol solution, 5 per cent, and iodine were used for preparatory toilet. The posterior vaginal wall was repaired with a continuous No. 1 catgut suture, the levatores ani and superficial perineal muscles with interrupted No. 2 catgut sutures, and the skin with interrupted nylon sutures (or catgut in a few cases). A rectal examination was always performed at the conclusion of the operation.

In 17 cases local infiltration of the Efocaine solution was employed. The solution was drawn up into a dry Labat syringe to avoid precipitation of the procaine base. The relative viscosity of the solution necessitates the use of a locking syringe if a narrow-gauge needle is to be used, and this is indeed preferable because it minimizes the risk of haematoma formation and pooling of the drug can be more easily avoided. The needle was inserted at approximately 1 cm. from the lower angle of the episiotomy, and the drug was injected into the subcutaneous tissue at a depth of $\frac{1}{4}$ to $\frac{1}{2}$ inch. A fine anaesthetic line was created parallel to the incision up to the muco-cutaneous junction. The infiltration is repeated on the opposite side to completely block the episiotomy area. When the patient is not under a general anaesthetic, a preliminary skin-wheal and infiltration of the subcutaneous tissue with aqueous procaine hydrochloride is required. A few of these conscious patients complained of a slight burning sensation at the site where Efocaine was introduced.

In 3 cases a longer needle was employed, and Efocaine was used to block the pudendal nerves on both sides.

The amount of anaesthetic used varied, but was never less than 8 ml. and never more than 12 ml.

Results

All patients were skin-tested each day with a sterile needle. The first case was a failure. On recovery from the general anaesthetic, the

patient complained of burning pain in the perineum. This pain passed off after 7–8 hours. Objectively there were patchy areas of insensitivity to pin-prick, but all sensation had returned to normal within 24 hours. The solution had evidently been injected too superficially.

Of the remaining 16 cases treated by local infiltration, the initial results were good. All these patients were free from pain, and were able to sit up in bed comfortably from the start. In 5 cases objective analgesia was patchy during the first 24 hours. The duration of analgesia varied. In 1 case sensation was recovered on the 4th day but in 2 the effect lasted 6 days, in 6 cases 7 days, in 3 cases 8 days, and in the remaining 4 the perineum was still partially anaesthetized on discharge from hospital.

The first case treated by pudendal block was only partially successful. A large area on the right side of the perineum was unaffected, but the left side was analgesic for 10 days. The remaining 2 cases were adequately blocked, and sensation did not recover for 8 days in 1, and 7 days in the other.

Complications

There were 3 cases of local sepsis. The first patient had severe cardiac disease, and her condition was so poor after delivery that repair of the episiotomy was delayed for 24 hours. The perineum healed without complication. On the 15th day she developed an abscess at the site of infiltration, which discharged spontaneously into the vagina. The second patient suffered a previous 3rd degree tear, and the perineum broke down on the 8th day. The third patient developed a mild superficial infection along the suture line not related to the infiltration site. Besides these cases, there were 3 patients who developed " flushed " perineums late in the puerperium, after removal of the sutures. There was local tenderness at the site of the Efocaine infiltration which cleared up within 24 hours without specific treatment.

Retention of urine occurred only once. On theoretical grounds a decrease in this complication would be expected, but the series is too small to form any conclusions on this point.

No generalized undesirable side-effects were observed.

Advantages

Relief of pain was especially gratifying to those patients who had had previous perineal suturing. These were unanimous in stating their approval. No other analgesics were required for any of the 20 patients. Removal of sutures was painless in all cases except the 2 in which sensation returned early. Breast feeding was facilitated, since the mothers could sit up properly in comfort.

Discussion

The 3 cases of local sepsis demand serious consideration. One case was very slight, and could have happened in any circumstances. The other 2 cases, although admittedly poorer risks, suggest that Efocaine may have tissue-irritating properties hitherto discounted (Weinberg, 1952). This would explain the peculiar " flushing " at the injection site late in the puerperium in the other 3 cases.

Infection may have been introduced because of poor technique, but I have followed up 24 cases of episiotomies personally repaired before and during the trial. There was no case of abscess or perineal breakdown. Local infiltration of the perineum with Efocaine entails extra manipulations and increases the time during which the tissues are exposed. These factors are known to increase the risk of inflammation. Blocking the pudendal nerve causes less local interference and may be preferable. Indeed Roualle (1952), in a study of 14 surgical cases, indicated that nerve-blocking with Efocaine is more efficient than local infiltration. This author did not encounter any local sepsis. Perhaps the daily exposure of the perineums for the purpose of skin testing was the determining fault.

Summary

A clinical trial of 20 cases is recorded in which Efocaine was used to relieve pain after episiotomy.

There were 2 failures, 1 fairly good result, and 17 good results in which prolonged postoperative analgesia was obtained.

The possibility that Efocaine may be a tissue-irritant and increase the local sepsis rate is suggested but not proven.

I would like to thank Dr. J. W. A. Hunter for the original suggestion of this trial, and Messrs. Crookes Laboratories for their generous supplies of Efocaine.

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OBSERVATIONS ON TOTAL LEUCOCYTE COUNTS DURING THIRTEEN CONSECUTIVE HUMAN MENSTRUAL CYCLES

BY

I. L. MACKINNON, M.B., Ch.B.

Senior Lecturer in Anatomy, King's College, University of London

THE possibility of the existence of a relation between the number of circulating leucocytes and the human menstrual cycle has long been appreciated. Dirks (1912) described a lymphocytosis at the bleeding phase of the cycle; Medlar (1929) concluded from his investigations that no relation existed; Rowe and Guagenty (1934) found that leucocytes tended to diminish in number during menstrual bleeding and to increase after its termination, but found no characteristic pattern; Mackinnon (1949) confirmed the finding of Rowe and Guagenty that leucocytes tend to diminish in number during the bleeding phase and to increase after its termination and, in addition, demonstrated a characteristic pattern in leucocyte counts for a group of women. He was, however, unable to obtain "significant" findings for any one woman.

The present investigation was made in order to find out if the total leucocyte counts of one female were "significantly" related to her menstrual cycle.

METHODS

Examination of one healthy woman, unmarried, aged 25, was made daily between 7 a.m. and 8 a.m. for a period of a year.

Oral temperature was taken before rising from bed with the object of gaining as much knowledge as possible of the events of the menstrual cycle. Immediately on rising blood was sampled by pulp stab and diluted by 20 to 1 prior to counting in a Thoma chamber.

In Table I total leucocyte numbers are arranged to display the individual counts for each day of the 13 consecutive menstrual cycles. Blank spaces denote days when, due to intercurrent infection or other causes, it was found impossible to take samples. Spaces filled in by dashes were outside the limits of cycles. For each day of the menstrual cycle arithmetic means of the total leucocyte counts and the standard deviations from them were calculated and recorded. In addition, arithmetic means and standard deviations were calculated and recorded for each successive group of 3 days. A graphic arrangement of the arithmetic means for each day of the cycle is presented in Fig. 1.

Daily oral temperatures for each day of the period of observation are recorded in Table II, which also contains the arithmetic means and standard deviations for each day, and for each consecutive 3 days, of the menstrual cycle. Graphic arrangement of oral temperatures for each day of the cycle is presented in Fig. 2.

"Significance" was ascribed to any two arithmetic means which differed from each other by more than twice the standard error of their difference, the standard error of the difference being $\frac{(S.D._1)^2}{n_1} + \frac{(S.D._2)^2}{n_2}$, where $S.D._1$ and $S.D._2$ are the standard deviations of the observations in the samples in question, and n_1 and n_2 the number of observations used to determine the means (Hill, 1950).

RESULTS

Table I shows that variations in the total leucocyte counts during the investigation ranged from 3,100 per c.mm. to 8,900 per c.mm., and that the menstrual cycles varied in length from 25 days to 29 days. The average total leucocyte count was calculated to be 5,300 per c.mm.

Fig. 1 illustrates the trend of the leucocyte counts during the mestrual cycle. It shows that counts are lowest at the 5th day and highest at the 24th day; that they rise gradually between

TABLE I

Total leucocyte counts (in hundreds) for each day of thirteen consecutive menstrual cycles, with standard deviations for each day, and for each successive three days.

Day of menstrual cycle	SUCCESSIVE MENSTRUAL CYCLES													Average count for each day	Standard deviation for each day	Average count for 3 days	Standard deviation for 3 days
	1	2	3	4	5	6	7	8	9	10	11	12	13				
1.	51	52	55	35		44	42	68			56	75		53	23		
2.	61	46	46	64		64	60	75		55	63	51		58	23	55.8	22.0
3.	75	48	55	35	65	57	65	60	74	45	61	57	39	56	22		
4.	72	52		49		58	55	55	66	46		50	42	54	21		
5.	52	37	60	53	65	40		59	47	44	48	47	38	50	15	52.4	17.6
6.	64	41	56		53	48				52		49		54	16		
7.	70	41	46	73		45			60		53		46	54	24		
8.		49		54		40		38	67	62		53	41	51	20	53.0	22.0
9.	78	42	68	65		60		54	47		36	45	41	53	24		
10.	48	40	60	53		34	65	40	61		50	49	81	53	21		
11.	40	39	56	78			46	65	66	63	58	51	79	58	21	56.4	24.0
12.		50	53				48	60	64	64	78	60		59	26		
13.	48	52		82			46		65	59	63	57		59	25		
14.	49	55	39	78		54	65		49	49				54	26	56.3	25.0
15.	42	48	50	75		60	38	61	56		68	67		56	24		
16.	47	40	54	58	68	42	50	70	89		56	57		57	24		
17.	48	38	56	85	48	62	56	82	60		73	55	52	59	24	56.5	24.0
18.	43			60	50	46	58		81	52	54	51	55	55	21		
19.		44	47	54	52			64	55	45	66	47	84	56	22		
20.		57	64	60	72	36	95	50		71	76	70		64	29	61.0	21.0
21.	43	50	62	60	64	44	72	79	50		89		60	63	27		
22.	48	31	46	82	55	70	77	65	81	75	59	80	45	63	23		
23.	55	47	63	70	49	54	60	67	60	89	53		70	61	23	63.1	18.0
24.	53		62		60	80	72	86	48	53		84	60	66	25		
25.	48		59		65	75	45		37	52	56	52	60	55	21		
26.	48	63	48	—	78		65	60	73	66	68	53	54	62	20	56.8	22.0
27.	39	53	55	—	63	34	55	—		57	70			53	24		
28.	37	—	—	—	58	—	—	—	—		—	—	—				
29.	—	—	—	—	—	—	—	—	—	59	—	—	—				

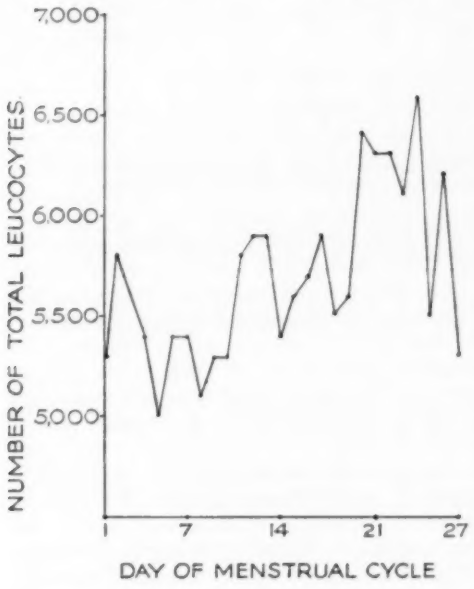

FIG. 1

Average number of total leucocytes for each day of the menstrual cycle.

the 5th and 24th days; that they fall during the bleeding phase and after the 24th day; and that they rise slightly during the 11th to 13th days.

Statistical comparison of the arithmetic means of the total leucocyte counts for each day of the cycle (Table I) by the estimation of the standard error of their differences shows that the only two which differ "significantly" are those of the 5th day and the 24th day. The standard error of difference between the means for these two days is 8, while the actual difference between the means is 16. A "significant" difference also exists between the means of the combined 4th–6th days and the combined 22nd–24th days, the standard error of their difference being 4.5, and their actual difference 10.7. The counts for the 11th to 13th days are not "significantly" different from the counts of any other group of three successive days, nor is there "significance" in the falls which take place during the bleeding phase or after the 24th day.

Fig. 2 shows that body temperature was at its lowest on the 12th day, and almost equally low on the 11th and 13th days, of the menstrual cycle. Ovulation probably occurred most commonly on these days (Corner, 1951). Until the time of ovulation oral temperature remained comparatively constant, but after ovulation it rose steeply to the 17th day and subsequently continued to rise, though at a slower pace, until the end of the cycle. Calculation of the standard error of the difference between the mean temperature on the 12th day and that of each of the other days of the cycle reveals that the 1st day is "significantly" different, and that the 17th and all subsequent days are "significantly" different, but that no "significant" difference exists between the 12th day and any day between the 1st and 17th.

Comparison between the graphs of the average leucocyte counts (Fig. 1) and prevailing oral temperature (Fig. 2) leaves no doubt that, although the total leucocyte counts and body temperature are higher in the later than in the earlier parts of the menstrual cycle, there is no direct relation between them. At the time when body tempera-

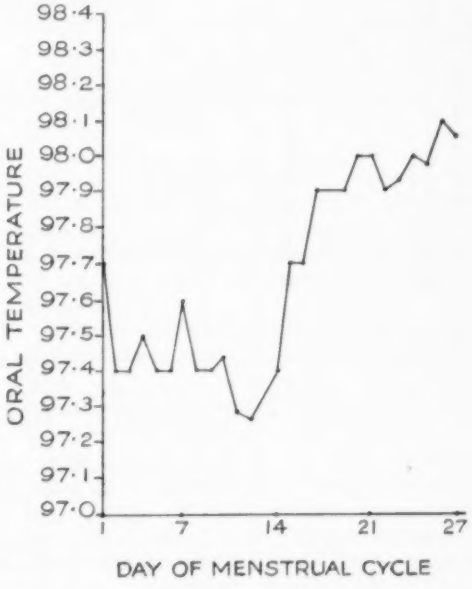

FIG. 2

Average oral temperature (Fahrenheit) for each day of the menstrual cycle.

TABLE II

Oral temperatures (in degrees Fahrenheit) for each day of thirteen menstrual cycles, with standard deviations for each day, and for each successive three days.

Day of menstrual cycle	SUCCESSIVE MENSTRUAL CYCLES													Average temperature for each day	Standard deviation for each day	Average temperature for 3 days	Standard deviation for 3 days
	1	2	3	4	5	6	7	8	9	10	11	12	13				
1.	97.6	97.6	97.4	97.6		97.9	97.8	97.8			97.5	97.9		97.7	0.17		
2.	97.8	97.6	97.4	97.6		97.2	97.2	97.2		97.4	97.0	97.6		97.4	0.27	97.5	0.22
3.	97.8	97.6	97.6	97.2	97.6	97.2	97.6	97.2	97.0	97.2	97.2	97.6	97.6	97.4	0.27		
4.	97.6	97.7		97.4		97.4	97.4	97.4	97.0	97.3		97.8	97.8	97.5	0.3		
5.	97.9	97.6	97.6	97.5	97.6	97.2		97.3	97.1	97.2	96.8	97.6	97.8	97.4	0.39	97.4	0.3
6.	97.6	97.4	97.0		97.6	97.2				97.3		97.6		97.4	0.3		
7.	97.6	97.4	97.4	97.6		97.0			98.4		97.4		98.0	97.6	0.4		
8.		97.6		97.3		97.2		97.4	97.6	97.0		97.4	97.8	97.4	0.27	97.46	0.33
9.	97.7	97.5	97.2	97.4		97.1		97.2	97.6		97.2	97.6	97.6	97.4	0.22		
10.	97.8	97.5	97.7	97.5		97.1	97.2	97.2	97.4		97.3	97.6	97.4	97.43	0.57		
11.	97.4	97.0	97.6	97.6			96.8	97.2	97.1	97.0	97.3	97.7	97.4	97.28	0.45	97.32	0.4
12.		97.4	97.8				97.4	97.1	97.2	97.0	96.8	97.4		97.26	0.47		
13.	97.4	97.6		98.0			97.0		97.0	96.9	97.0	97.5		97.34	0.6		
14.	97.4	97.7	97.5	97.8		97.6	97.2		97.0	97.0				97.4	0.6	97.48	0.3
15.	97.4	97.8	97.8	98.0		97.6	98.0	97.6	97.8		97.4	97.2		97.7	0.5		
16.	97.9	98.0	97.9	98.0	97.6	97.6	98.0	97.4	97.0		97.8	97.8		97.7	0.4		
17.	98.0	98.2	98.2	97.6	97.6	97.8	98.0	97.8	97.6		97.6	98.2	98.4	97.9	0.45	97.83	0.33
18.	97.9			98.2	97.6	98.2	97.8		98.0	97.6	97.4	98.0	98.0	97.9	0.31		
19.		98.2	98.0	98.0	97.6			97.8	97.8	97.5	97.6	98.0	98.4	97.9	0.37		
20.		98.2	98.0	98.2	97.8	98.0	98.4	97.9		97.7	97.8	98.0		98.0	0.4	97.97	0.3
21.	98.2	98.4	97.8	98.2	97.8	97.8	97.6	97.9	97.8		98.3		98.2	98.0	0.4		
22.	98.2	98.2	97.8	98.0	97.8	97.8	97.3	97.9	97.8	97.6	97.8	98.2	98.2	97.9	0.36		
23.	98.0	98.4	98.0	98.0	97.6	97.8	97.8	98.0	97.9	97.7	98.0		98.0	97.93	0.23	97.94	0.3
24.	98.2		98.2		97.6	97.8	98.0	98.0	97.9	97.7		98.2	98.4	98.0	0.41		
25.	98.0		98,0		97.6	97.4	98.1		97.6	97.9	98.2	98.2	98.8	97.98	0.5		
26.	97.9	98.3	98.3	—	97.8		98.0	98.0	97.7	98.0	98.3	98.2	98.4	98.1	0.48	98.09	0.33
27.	98.2	98.4	98.0	—	97.8	97.8	98.4	—		97.8	98.0			98.05	0.47		
28.	98.2	—	—	—	97.8	—	—	—	—		—	—	—				
29.	—	—	—	—	—	—	—	—	—	97.8	—	—	—				

ture is at its lowest (11th–13th days) there is in fact a leucocytosis.

Discussion

The average total leucocyte count during the investigation was 5,300 per c.mm., the range extending from a minimum of 3,100 per c.mm. to a maximum of 8,900 per c.mm. Both the average count and the range are similar to those obtained under basal conditions by Shaw (1927) and by Bryan, Chastain and Garrey (1935) and can be regarded as normal basal counts.

Comparison of the change in leucocyte counts obtained during the present investigations on one woman (Fig. 1) with those obtained previously from a group of women (Mackinnon, 1949) demonstrates that, although the graph for the group of women is set at a higher level than the graph for the single woman, there is a marked similarity in character between them. No doubt the higher average counts obtained from the group of women were due to sampling under conditions which were not strictly basal (Bryan, Chastain and Garrey, 1935). The similarity in character between the two graphs appears to be due to the presence in each of two clear-cut features—a fall in the total leucocyte counts during menstrual bleeding, and a subsequent steady rise until late in the cycle.

Statistical investigations of leucocyte numbers are inevitably linked with high standard deviations because wide variations occur in total leucocyte counts for no apparent reason (Medlar, 1936). Absence of " significance " does not exclude a leucocyte count from being characteristic of a particular part of the menstrual cycle and, although " significance " is confined in this investigation to the difference between the counts at the 4th–6th days and the 22nd–24th days, the similarity in the behaviour of leucocyte numbers in the present investigation to their behaviour in a previous investigation (Mackinnon, 1949) suggests that features common to both, for example the fall during menstrual bleeding, are not due to chance. The possibility of the existence of an ovulatory leucocytosis must be borne in mind in view of the synchronous relation of a leucocytosis at the 11th–13th days of the cycle (Fig. 1) to the time of minimal body temperature (Fig. 2).

A fall in body temperature at some point between the 8th and 14th days, and commonly between the 11th and 13th days, is a recognized characteristic of the human menstrual cycle, and the implication that ovulation occurs at this time is adopted in obstetrical practice. In view of this, the failure during the present investigation to obtain " significance " between the average temperature on the 12th day and the neighbouring days of the cycle supports the thesis that, although it is desirable to obtain " significance " for any record of events, it is unwise to ignore trends which lack " significance " but appear to be characteristic.

It has been suggested that the changes in total leucocyte counts during the menstrual cycle are associated with alterations in body temperature resulting from alterations in blood oestrin (Mackinnon, 1949). The dissimilarity in the graphs of total leucocyte counts (Fig. 1) and prevailing body temperature (Fig. 2) makes it abundantly clear that this is not the case. The changes in leucocyte counts do, however, appear to be associated with the presumptive changes in blood oestrin (Young, 1950); and the possibility that they are influenced by blood gonadotrophic hormone at the time of ovulation (Wolf, 1939), or by blood progesterone (Young, 1950) or body temperature during the latter half of the cycle, cannot be excluded.

Summary

(1) Total leucocyte counts and oral temperatures were recorded daily, under basal conditions, for one healthy unmarried woman, aged 25, during a period of a year, incorporating 13 menstrual cycles.

(2) The variations in total leucocyte counts during the menstrual cycle were examined statistically and " significance " demonstrated between the low counts of the 4th to 6th days and the high counts of the 22nd to 24th days.

(3) Comparison of the variations in the total leucocyte counts with those of the prevailing oral temperatures indicates that body temperature is not directly related to the changes in leucocyte counts which occur during the menstrual cycle.

(4) It is suggested that variations in total leucocyte counts during the human menstrual cycle are related to those of the blood oestrin.

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EOSINOPHILS AND PREGNANCY

BY

D. W. DAWSON, M.B., Ch.B.

Registrar in Clinical Pathology, General Hospital, Salisbury

THE fall in the circulating eosinophils after an injection of anterior corticotrophic hormone (A.C.T.H.) and in various types of stress is often employed as an index of adrenocortical activity. In patients with Addison's disease, however, cortisone but not A.C.T.H. produces similar results (Thorn, Prunty and Forsham, 1947; Dougherty and White, 1947). With prolonged administration of A.C.T.H. there is a large and sustained fall in circulating eosinophils (Prunty, 1950). The eosinopenia is mediated therefore through adrenocortical stimulation by the anterior pituitary. Eosinopenia is a frequent finding in Cushing's syndrome (De La Balze, Reifenstein and Albright, 1946). The circulating eosinophils are thus probably an indication of endogenous pituitary-adrenal activity. Davis and Hulit (1949) reported the finding of eosinopenia in pregnancy.

During pregnancy there is hypertrophy and excessive activity of the anterior pituitary and adrenal cortex. The anterior pituitary shows an increase in both basophil and acidophil cells (Huggett, 1950). It is not known whether the pituitary is essential for the maintenance of pregnancy in the human though it is so in the rabbit and bitch (Greene, 1948). The site of origin of the various hormones of the anterior pituitary is not known with certainty but it is probable that corticotrophin (A.C.T.H.) is produced by the basophils, these cells also being the presumed source of gonadotrophic hormone. It has been found, however, that the anterior pituitary contains practically no gonadotrophic hormone during the greater part of pregnancy (Greene, 1948). The increase in basophils of the anterior pituitary in pregnancy is perhaps due to increased A.C.T.H. production.

Because of this evidence of increased pituitary and adrenal activity in pregnancy, and of the effect of such activity upon the circulating eosinophils, studies of the latter in pregnancy were undertaken.

METHOD

A total of 481 eosinophil counts were carried out on 75 patients who went through normal pregnancies, and 218 counts in 63 normal puerperia. Forty-one of these patients were seen 6 weeks after delivery to obtain their normal non-pregnant counts. Seven counts were done during labour. One hundred and eight counts were done on 14 toxaemias of pregnancy.

Blood was obtained by fingerprick to avoid the errors of ear blood as indicated by Lucey (1950). A dilution of 1:10 was made with the staining solution. In the early part of the investigation Randolph's fluid (1949) was used, in the latter part MacFarlane and Cecil's modification of Pilot's method (MacFarlane and Cecil, 1951) was substituted.

Two single-chamber Fuchs-Rosenthal counting chambers were flooded and the cells in the entire ruled area counted. The number of eosinophils per c.mm. blood was obtained by multiplying the number counted by 1.6.

Nearly all samples were collected between 10 a.m. and 11 a.m. This was done to eliminate the normal diurnal variation (Rud, 1947; Best and Samter, 1951) though the minute-to-minute fluctuations that may occur could not be excluded. The first sample from each normal patient was collected in the afternoon since this was the time when the patients attended their first clinic. Repeated counts were done on each patient, for only then could conclusions regarding pituitary-adrenal function be drawn (Best and Samter, 1951).

RESULTS

Pregnancy: Of the 75 normal pregnancies there were 34 primigravidae, 22 in their second

TABLE I
Eosinophil counts in pregnancy

Week of pregnancy	Numbers of counts performed	Mean eosinophil count. Eosinophils per c.mm.
10–14	34	88
15–19	56	90
20–24	67	96
25–29	90	92
30–34	102	85
35–39	119	91
40	17	80

pregnancy, and 19 multiparae, who had undergone at least 2 previous pregnancies. The average for all these patients was 90 eosinophils per c.mm. No significant difference was found between the three groups. The mean counts at progressive times in pregnancy are shown in Table I. There is no significant difference between these counts. Forty-one patients seen 6 weeks after delivery when they were healthy clinically gave a mean count of 183 eosinophils per c.mm. This was taken as the average for normal non-pregnant women.

During pregnancy there is an average fall of 51 per cent in the eosinophil count which is uniform throughout gestation. The percentage fall in the eosinophil count during pregnancy showed a direct relationship to the normal level (taken as the average of the counts on the 10th day postpartum and in the 6th week after delivery). This is indicated in Fig. 1. No connexion was established between the degree of fall and the clinical course of pregnancy, and normal pregnancies were associated with both high and low eosinophil counts. The eosinophil count was fairly constant during pregnancy in each case but unexplained variations occurred occasionally.

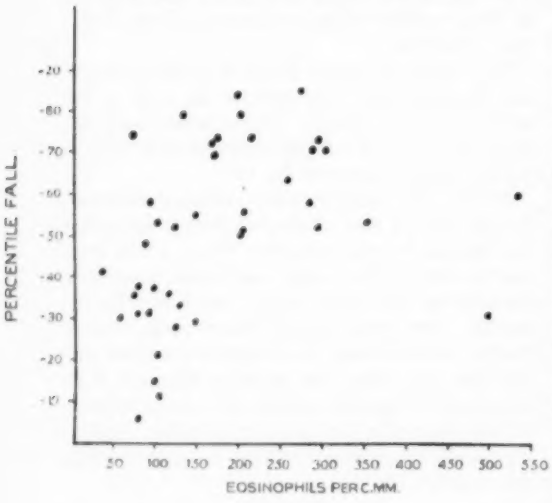

FIG. 1

Showing the relationship between the normal eosinophil level and the percentile fall in pregnancy (41 cases)

One patient, gravida-2, twice exhibited an absolute eosinopenia during pregnancy. Her average count was 11 eosinophils per c.mm. (the mean of 9 counts). Pregnancy, labour and the puerperium were uneventful. One patient, gravida-2, developed thrombophlebitis in the 33rd week of pregnancy which resolved after 3 weeks rest. Her average count before and after this complication was 106 eosinophils per c.mm.; while the inflammation was present the count averaged 40 per c.mm.

Labour. In the few patients examined a marked eosinopenia was found.

Puerperium. A clear pattern was evident in the eosinophil count in the first 10 days postpartum, as seen in Fig. 2. In both primiparae and multiparae the eosinophils reached a peak on the 4th day and fell again gradually until at about the 7th day a similar level to that found at the follow-up clinic was reached. Although there was no statistical difference between the 5th and 10th day figures, nearly all cases gave a higher count on the earlier day. The curve in Fig. 2 applies to both breast-feeding and non-breast-feeding patients between whom no difference was found in this period. The height of the eosinophil rise was related to the pregnancy level, being higher in those with higher pregnancy counts.

At the 6th postpartum week the breast-feeding mothers had an average eosinophil count of 167 per c.mm. (30 patients), the non-breast-feeding ones an average of 231 (11 patients). The numbers examined were too few for these figures to be statistically different.

The patient with thrombophlebitis during

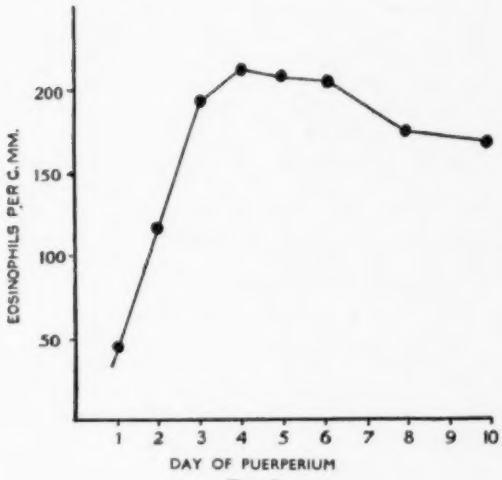

FIG. 2

Showing the pattern of the eosinophil count in the puerperium.

pregnancy suffered from further venous inflammation in the puerperium. On the 6th day postpartum her count was 60 eosinophils per c.mm. On this day her leg became painful due to further phlebitis. At the 6th week her count was 296 eosinophils per c.mm. At this time she was quite well.

Toxaemias of pregnancy. The mean pregnancy count in 14 cases was 86 eosinophils per c.mm., a 60 per cent fall from their postnatal figures. Four of these patients were examined before and after the onset of the toxaemia and showed no difference in their counts. Insufficient cases were studied for the production of a graph of the postpartum eosinophil count but each individual case presented a rise and fall like that in normal pregnancy.

DISCUSSION

Pregnancy

The findings in pregnancy confirm those of Davis and Hulit (1949) that there is an eosinopenia throughout its duration, and that the fall in the circulating eosinophils is of similar degree throughout gestation. The time of onset of the eosinopenia was not discovered though it occurs early, since the counts in the 10th to 14th weeks were the same as later ones. When considering the cause of the fall in the circulating eosinophils, the pituitary-adrenal system, for the reasons stated earlier, naturally draws attention. However, the urinary corticoids excretion rises to about twice the normal value at about the 10th week of pregnancy, falls again, and then rises to four times the normal value during the third trimester (Venning, 1946). If this indicates increased adrenocortical activity the eosinophil count does not reflect it to any significant degree.

Kellgren *et al.* (1952) studied the eosinophil response to A.C.T.H. and cortisone in rheumatoid arthritis, and suggest that the degree of response to a standard dose may to some extent be a reflection of the level of the endogenous production. In this series those patients with a higher percentage fall in the eosinophil count were usually those with a higher normal count, as seen in Fig. 1. If a high normal eosinophil count indicates a low basal output of adrenal hormones then the stress of pregnancy may produce a good response in the pituitary-adrenal system. On the other hand, a person with a low normal eosinophil count may have a high endogenous production and a similar stress may not call for so great a response, there being no need for a large additional output of hormones. Prunty (1950), however, considers that the basal level of the circulating eosinophils is governed by factors other than the adrenal cortex, noting that though the eosinophil count in Addison's disease may be high this is not statistically significant. This is probably so, but the direct relationship between the basal level and the response to the stress of pregnancy suggests that the adrenals play some part in controlling the normal level and also in causing the pregnancy eosinopenia. It is seen that the eosinophils fall very early in pregnancy, and this may be a continuation of the mild eosinopenia found by Davis and Hulit (1949) in the luteal phase of the menstrual cycle. No actual figures were reported and it is difficult to determine from their graph how real or large this fall actually is. Thorn *et al.* (1949) state that only the 11–17 oxysteroids affect eosinophil and lymphoid tissue, and it has been shown that gonadectomy has no appreciable

effect on the circulating eosinophils in normal dogs (Simms, Pfeiffenberger and Heinbecker, 1951), so it appears that progesterone is not responsible for any such fall. Whatever the cause of the eosinopenia in pregnancy, the effect of the pituitary-adrenal system is seen in labour when a marked eosinopenia occurs. According to Davis and Hulit (1949) eosinophils disappear from the circulation during the third stage. The effect of these hormones is also evident in complications of pregnancy such as thrombophlebitis. The fact that a further fall in the eosinophil level can occur with such a complication indicates that the circulating eosinophils can show a response to additional stress, and it is curious, therefore, that they do not fall progressively as pregnancy continues.

Normal pregnancies occurred with both high and low eosinophil counts. This is of interest when observing that pregnancy may occur in Addison's disease. When it does the disease is usually aggravated thereby, but often pregnancy goes to term. Labour is not usually prolonged or difficult but crises are common in the puerperium (Van Zwanenberg, 1945).

The pattern of the circulating eosinophils is similar to that described by Gabrilove (1950) following operative procedures. Nearly all the patients showed a maximum level on the 4th day, the counts rising sharply until this time, and then gradually falling off until the normal "non-pregnant" level was reached. The height of the eosinophil rise after labour was unrelated to the duration of labour, but was in direct proportion to the pregnancy level, being higher in those with the higher pregnancy counts. The rise above the "basal level" was seen by Gabrilove following surgery and was attributed by him to a diminution in corticoid secretion, the previous eosinopenia reflecting an increased corticosterone output.

Sevitt (1951) in following the leucocyte changes in patients suffering from burns correlated the area of body burned with the duration of eosinopenia, using this term for levels under 40 per c.mm. He considered a rise before the expected day indicated adrenal cortical failure. In this series of puerperal women the duration of such an eosinopenia, deduced from Fig. 2, is about 1 day. It is not therefore possible to assess an abnormally early eosinophil rise, owing to the short duration of the normal eosinopenia. Presumably the demand on the adrenals which occurs during labour terminates soon afterwards and does not continue as in the case of extensive burns.

Davis and Hulit (1949) suggested that the eosinophil response to labour is much more sensitive than the total white cell count since the latter has not always returned to the normal non-pregnant level at the 9th postpartum day, but from this study of normal puerperia it is seen that the great variability in eosinophil levels makes such a count of little practical use. However, if the eosinophil level in pregnancy is known (and by this is not meant the result of one estimation), then a rise of less than the expected degree by the 4th day may indicate a pathological process. This was the case with the patient who developed thrombophlebitis. In general the count should be double the pregnancy level by this day, but with low pregnancy levels this rise is not so great (Fig. 1).

Toxaemias of pregnancy

The results in the few cases examined show that there is no significant difference in the eosinophil count between normal and toxaemic pregnancies. This confirms the findings of Bernstine and de Andino (1952).

Two points are worthy of comment. Firstly Davis and Hulit (1949) reported the disappearance of eosinophils from the circulation during the convulsions in 2 cases of eclampsia. However, in one patient of this series there was complete eosinopenia twice during a normal pregnancy, so that the finding of an absolute eosinopenia in eclampsia does not necessarily indicate abnormal adrenal function. Further cases need studying to determine whether this is a constant feature of eclampsia.

Secondly, toxaemias of pregnancy have been treated with cortisone with favourable results (Moore *et al.*, 1951). The outcome in 8 cases so treated was independent of the degree of eosinopenia produced by the hormone. It would be of interest to note the eosinophil count before treatment with the hormone in future cases, and to compare the clinical response with the eosinophil response.

Summary

The eosinophil response to pregnancy was studied in 75 normal cases and in 14 cases of toxaemia.

The constant eosinopenia observed throughout pregnancy is confirmed. It is considered that both the basal, normal, non-pregnant eosinophil level and the level in pregnancy are controlled in part by the adrenal cortex, but that other factors also operate. An eosinophil pattern in the puerperium is described, similar to that following surgical operations. The use of eosinophil counts to assess the complications of the puerperium is considered to be of little value owing to the wide normal variations.

I should like to thank Dr. J. C. Gordon for allowing me to make this investigation on patients under his care, and for his interest in the work. My thanks are also due to Mrs. E. J. Morris for technical assistance.

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ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

A MEETING of the Council was held in the College House on Saturday, 25th July, 1953, with the President, Mr. Arthur A. Gemmell, in the Chair.

The following officers were re-elected:

President

Arthur A. Gemmell, Esq., *M.C.*, T.D., M.A., M.D., F.R.C.S.E., P.R.C.O.G.

Vice-Presidents

Prof. Gilbert Innes Strachan, *C.B.E.*, M.D., F.R.C.P., F.R.C.S., F.R.C.O.G.
Arthur James McNair, Esq., M.A., M.B., B.Ch., F.R.C.S., F.R.C.O.G.

Honorary Treasurer

Arthur Capel Herbert Bell., Esq., M.B., B.S., F.R.C.S., Hon.M.M.S.A., F.R.C.O.G.

Honorary Secretary

Humphrey G. E. Arthure, Esq., M.D., F.R.C.S., F.R.C.O.G.

Honorary Librarian

Arthur James McNair, Esq., M.A., M.B., B.Ch., F.R.C.S., F.R.C.O.G.

Honorary Curator of the Museum

Aleck William Bourne, Esq., M.A., M.B., B.Ch., F.R.C.S., F.R.C.O.G.

Honorary Treasurer, Canadian Regional Council

William Rodgers Foote, Esq., B.A., M.D., C.M., F.R.C.S., F.A.C.S., M.R.C.O.G.

The following officers were elected:

Honorary Treasurer, Australian Regional Council

John Nicholson Chesterman, Esq., M.B., Ch.M., F.R.C.S.E., F.R.A.C.S., F.R.C.O.G.

Honorary Treasurer, New Zealand Regional Council

James Edinett Giesen, Esq., M.D., B.S., M.R.C.S., L.R.C.P., M.R.C.O.G.

The following was admitted to the Membership:

Donald Stewart Burris

The Bernard Baron Research Scholarship has been awarded to Stanley Albert Way, Esq., M.R.C.S., L.R.C.P., F.R.C.O.G., of Newcastle, for research on problems connected with the early diagnosis of cancer in women.

The following were elected to the Membership:

Louis Julius Abramowitz
Subrahmanyan Alankaram
William John Ronald Anderson
Geoffrey Spencer Andrew
Amiya Kumar Bose
John Charles Brace
Edward Rodney Broadberry
Timothy John Buckley
Samuel Burke
Robert Keltie Burt
James Grant Cameron
Rory Shaun Casement
Po Wong Christina Chow
Maureen Daly Connolly
Robert Logan Edwards
Michael Brendan Flanagan
Frank Menzies Cameron Forster
Kathleen May Frith
Michael Cameron Gordon Grant
Peter Brutus Guastalla
Reginald Henry James Hamlin
John William Simmons Harris
Cyrus Arvon Jones
Rees Lloyd Jones
Ian Ross Macdonald
Betty Mallace
Gerald Arthur Manly
Donald Norwood Menzies
Maurice Cecil Michelow
John Nattrass
Hugh H. Neifeld
Francois Nicolas Neser
James Patrick O'Dwyer
Dharma Rau Patnaik
Clara Phillips
Basil George Pickles
William Rotheram
James Steel Scott
James Marshall Stewart
Ronald Anderson Struthers
Valerie Mary Thompson
Cyril Joseph Thornberry
Harry Ulman
Chester Gilmore Wilson

A MEETING of the Council was held in the College House on Saturday, 26th September, 1953, with the President, Mr. Arthur A. Gemmell, in the Chair.

The following awards were made:

Leverhulme Research Scholarships for 1954
Ian Donald.
Joseph Gardiner.
Matthew Lindsay Paterson.

William Blair-Bell Memorial Lectureships for 1954
Thomas Everard Christopher Barns.
Ian Donald.

NOTICE

AWARD FOR OUTSTANDING RESEARCH IN THE FIELD OF INFERTILITY

The American Society for the Study of Sterility announces the opening of the 1954 contest for the most outstanding contribution to the subject of infertility and sterility. The winner will receive a cash award of one thousand dollars, and the essay will appear on the programme of the 1954 meeting of the Society. Essays submitted in this competition must be received not later than 1st March, 1954. For full particulars concerning requirements of this competition, address The American Society for the Study of Sterility, c/o Dr. Herbert H. Thomas, Secretary, 920 South 19th Street, Birmingham, Alabama.

The author should append on a separate sheet of paper a short biographical sketch of himself and include a photograph to be used in the necessary publicity should he be the winner of the award.

HOSPITAL REPORTS

BY

ANTHONY W. PURDIE, M.B., F.R.C.O.G.

MEDICAL REPORT OF THE GLASGOW ROYAL MATERNITY AND WOMEN'S HOSPITAL FOR THE YEAR 1949

THIS is the twenty-fourth annual report and is presented in a form closely allied to that recommended by the Royal College of Obstetricians and Gynaecologists. The hospital contains 165 beds exclusive of 17 labour ward beds. During the year there were 4,452 adult admissions; there were 3,130 deliveries in the hospital, 85 patients were admitted after delivery and there were 430 cases of abortion. There were 29 maternal deaths (9.29 per 1,000 live and stillbirths), the stillbirth rate was 72.6 per 1,000 live and stillbirths and the neonatal death rate 29.9 per 1,000 live births. The hospital admits a high proportion of abnormal cases, as indeed it would have to do for these results to be accepted. It is said that the high proportion of abnormal cases has diminished slightly over the past few years owing to the expansion of the obstetric services both in the city and in the outlying areas.

Seven of the maternal deaths were due to heart disease, 2 among booked patients and 5 in non-booked patients. The details given of these fatal cases emphasize again how serious heart disease in pregnancy can be and the need for close co-operation between all concerned in the care of those patients as well as that of the patient herself. In another 7 fatal cases post-operative shock, post-operative collapse or post-operative cardiac failure was the cause of death. In general this should be an avoidable cause of death.

A detailed study of this report dealing with a wealth of obstetric material would fully repay the reader.

MATERNITY REPORT, WOOLWICH GROUP HOSPITAL MANAGEMENT COMMITTEE FOR THE YEAR 1951

THE report consists of statistical summaries from five maternity hospitals in the Woolwich Group. All primigravidae requesting admission are booked for confinement; others selected for admission are those with bad obstetric histories and those whose home conditions would make domiciliary confinement unsuitable.

There were 3,498 deliveries during the year with 3 maternal deaths. Of these, 1 was due to a fatal blood transfusion reaction, 1 to subarachnoid haemorrhage 11 hours after delivery but an autopsy does not appear to have been done, while 1 died under general anaesthesia (pentothal, nitrous oxide and trilene) during classical Caesarean section for obstructed labour due to uterine fibroid in a patient with marked hypertension. Among the cases of special interest is one of placenta praevia in which the spontaneous birth of the placenta was followed by the birth in a caul of a living premature infant which survived ultimately.

The stillbirth rate was 15.8 per 1,000 live and stillbirths and the neonatal death rate was 14.9 per 1,000 live births.

CLINICAL REPORT OF CHELSEA HOSPITAL FOR WOMEN, LONDON, S.W.3, FOR THE YEAR 1950

THIS report consists of four tables giving respectively a general analysis of the year's work, the classification of cases admitted, the abdominal operations performed, and the non-abdominal operations performed; an additional table consists of special reports relating to deaths. In addition there is a Cancer Report summarizing all the malignant cases seen in 1950, and a Report on the Department of Pathology by its Director for the year 1950. There were 17 deaths during the year of which 15 occurred in patients with advanced malignant disease.

CLINICAL REPORT OF THE NATIONAL MATERNITY HOSPITAL, DUBLIN, FOR THE YEAR 1951

THE hospital contains 132 beds of which 21 are antenatal, 103 postnatal, and 2 isolation. There were 4,696 admissions with 4,162 deliveries. Assuming that all the postnatal and isolation beds were in constant use the average stay in hospital after delivery would be 9.7 days. There were 376 extern deliveries. There were 15 maternal deaths in the hospital (3.6 per 1,000 deliveries) but none on the district. The stillbirth rate was 3.89 per cent, and the neonatal death rate 2 per cent.

As is customary, the Master's survey, which in this case occupies 17 pages, is an outstanding feature of the report. Here the year's results are criticized, policies explained, considered opinions and impressions recorded, and future intentions indicated. While it is unlikely that the reader will agree with all the Master's views the survey and report merit careful consideration.

CLINICAL REPORT, MATERNITY DEPARTMENT, OUR LADY OF LOURDES HOSPITAL, DROGHEDA, EIRE, FOR THE YEAR 1951

THE present hospital (it is hoped that a new hospital will shortly be built) contains 46 maternity beds (6 antenatal, 38 postnatal and 2 isolation). During the year there were 1,281 admissions to the maternity beds with 1,213 deliveries. It is stated in the Foreword that there were no maternal deaths. As only 55 per cent of the patients attend the hospital for antenatal care tribute is paid to the general practitioners who undertake the antenatal care of the rest; other helpful factors are stated to be the high standard of nutrition of the patients and the assistance of the National Blood Transfusion Service. A maternal death does appear (Reg. No. B6097) in Table 1, however. The patient suffering from tuberculous meningitis was admitted "for delivery with advanced disease and transferred afterwards for further treatment". While, doubtless, this would be classified as an unavoidable death it should be recorded as a maternal death and full details given. There were 35 stillbirths and 19 neonatal deaths, giving a combined foetal loss of 4.5 per cent.

Postpartum haemorrhage (Table 21) is said to have occurred in 6 cases (0.5 per cent). From the next table (Table 22) it appears that manual removal of the placenta was performed on 19 occasions. While none of the 6 cases of postpartum haemorrhage in Table 21 appear in Table 22, study of Table 22 shows that in at least 5 cases the manual removal was performed because of postpartum haemorrhage. The incidence of postpartum haemorrhage, while not high, would appear to be about twice that claimed.

In Table 2 details are given of 78 cases of complete abortion. In 52 of these the maturity of the pregnancy was not more than 14 weeks. This is rather a surprising collection of cases of complete abortion, but, as the method of treatment is not given, it is not possible to deduce if, on admission, abortion in any of these cases was in fact incomplete or in process.

A brief numerical account of 83 gynaecological cases admitted and the operations performed, along with the numbers of the pathological specimens examined, concludes the report.

REPORT OF THE PENINSULA MATERNITY HOSPITAL, CAPE TOWN, FOR THE YEAR 1949

DURING the year 2,205 patients were admitted to the hospital; these were classified racially as European 25 per cent, Cape Coloured 60 per cent, and Native 15 per cent, and among them there were 1,942 deliveries. In addition 634 patients were delivered on the district.

There were 4 maternal deaths. The first died of suppurative pyelonephritis; although the detailed account does not mention it the surmise is that she died undelivered. The second had pre-eclampsia and died 10 hours after delivery but the description given (which contains a number of obvious minor errors) does not make the cause of death clear and autopsy was refused. The third had eclampsia but the case does not appear in the eclampsia table and no maternal death is shown in the eclampsia table. In the fourth the cause of death was central placenta praevia.

The report contains many inaccuracies and evidences of carelessness in compilation. We are told on page 18 that there were 2 cases of abdominal hysterectomy for gross hypertension in early pregnancy. Details of these hysterectomies cannot be found but study of the detailed table following shows one case described as having hysterotomy at 28 weeks with a deadborn foetus, and one as having Caesarean section at 25 weeks resulting in a stillbirth. In the abortion table the result is described as stillbirth on 3 occasions. On page 40 we find that there were 40 cases of accidental haemorrhage and "in 10 cases there was pre-eclamptic toxaemia, essential hypertension and chronic nephritis." If this is to be taken literally surely these 10 cases would merit a publication devoted to them. On the same page the reader is referred to "cases of interest" but no such section can be found in the report. Similar errors can be found throughout the whole report.

While it is evident from a study of the report that, despite the errors in the report, a high standard of obstetrics obtains in the hospital, it is a little surprising to find that in 6 cases of Failed Forceps the failure occurred in 5 of these patients after admission to the hospital.

TWELFTH REPORT FROM THE DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, UNIVERSITY OF OTAGO (DUNEDIN), NEW ZEALAND

THIS report deals with 1,000 consecutive deliveries and the concurrent gynaecological work. The period covered is from August 1949 to September 1950 inclusive.

In the obstetric section there were 2 maternal deaths each in a non-booked patient. One, a second gravida, died of pulmonary embolism 3 days after an elective classical Caesarean section for contracted pelvis. The other died undelivered of severe accidental antepartum haemorrhage in what appears to have been a neglected case of pre-eclampsia. Strangely enough this fatal case does not appear in the Toxaemia table nor among the brief figures given for Accidental Haemorrhage; under both of these headings it is erroneously stated that the maternal mortality was nil.

The report as a whole is rather sketchy.

ANNUAL REPORT FROM THE DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, UNIVERSITY OF OTAGO, NEW ZEALAND, FOR THE YEAR 1951

THIS is the first report to be issued from the department since Professor J. L. Wright succeeded Sir Bernard

Dawson in the Chair of Obstetrics and Gynaecology. The practice of basing the report upon 1,000 consecutives deliveries has been abandoned and the report will now be issued annually. During the year there were 828 deliveries of which approximately 75 per cent were booked cases and 25 per cent non-booked. There were no maternal deaths. Among the 837 babies born there were 15 stillbirths and 14 neonatal deaths. In the gynaecological section there were 591 admissions among which there were 8 deaths; of these, 6 were from malignant conditions and 2 occurred following Fothergill operations for genital prolapse—one from heart failure on the third day and one from pulmonary embolism on the tenth day after operation.

The format of the report appears to be undergoing some change. More tables showing single case data are included and fresh matter such as prolonged labour and diabetic pregnancy is included.

The size of page is more than double that used in its predecessors and it seems rather large for an essentially small report.

154TH ANNUAL REPORT OF THE SOCIETY OF THE LYING-IN HOSPITAL OF THE CITY OF NEW YORK, FOR THE YEAR 1952

THIS report consists of statistics in connexion with 5,190 adult discharges from 127 obstetric beds and 1,937 discharges from 80 gynaecological beds. In a 9-page survey the Obstetrician and Gynaecologist-in-Chief makes a critical review of the year's work and considers the trends in the 20 years in which, since 1932, the Lying-in Hospital has occupied its present site.

The year's achievement has been most satisfactory. There were 4,148 deliveries with 4 maternal deaths—1 due to postpartum eclampsia and cerebral haemorrhage, 1 to acute nephritis, and 2 due to cancer of the breast. Of 4,194 infants born, 52 were classed as dead-born and there were 54 neonatal deaths, making a total foetal loss of 2.5 per 100 total births.

The incidence of forceps delivery is 27.3 per cent and of Caesarean section 5.1 per cent. To those accustomed to conservative obstetrics it is a little surprising to read: "The result to infants in terms of mortality in certain vaginal operative deliveries, . . . shows steady improvement and compares favourably with results obtained in spontaneously delivered infants. Actually in recent years, for example, the fetal mortality was less in low forceps operations than when the infant was spontaneously delivered." There are interesting graphs on this subject showing the 20-year trends.

This is a well-prepared and provocative report.

ANNUAL REPORT OF THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY (BELLEVUE HOSPITAL), NEW YORK, FROM 1ST JUNE, 1951, TO 31ST MAY, 1952.

THIS in fact consists of two reports, one from the Department of Obstetrics and one from the Department of Gynecology. Each consists of some 14–15 loose pages of printed typescript stapled together.

The obstetric report appears to have been compiled from individual case punch cards, the totals from which are recorded on working sheets, which are then typed in fair and better set out. Both fair and rough copy sheets have been printed and circulated, for much of the same information is given twice and the working sheets are full of directions such as "check at least one item in each group", "check numbers 0–3 only if pelvis has been X-rayed", "add appropriate number for presentation of twin B", "if stillbirth is circled it must be circled in two categories" and so on.

While the standard of the medical work in the hospital is high this report continues year by year to be issued in a form not worthy of the hospital. It may be that no member of the medical staff assumes responsibility for it.

CLINICAL REPORT OF THE DEPARTMENT OF OBSTETRICS OF THE NORTH MIDDLESEX HOSPITAL, LONDON, FOR THE YEAR 1949

THIS general hospital contains 140 obstetrical and 61 gynaecological beds. This Report, the first to be published, is concerned with the work carried out in the Obstetrical Department. Of the total of 140 beds, 102 (31 antenatal and 71 lying-in) are in the main hospital, whilst 38 are in the annexe at Finchley, 7 miles distant. There is a special department for premature babies, to which are admitted both babies born in the hospital and annexe and those delivered at home. Only those women for whom a normal delivery is expected are admitted to the annexe. Few patients are transferred from the annexe to the main hospital, chiefly those requiring abdominal section.

Four antenatal clinics are held weekly at the hospital. To these patients are referred from Local Authority Clinics or by their own doctors with a view to booking for hospital or for special consultation. Routine antenatal care is thereafter given by the Local Authority Clinic or, in some cases, by the private doctor. Some special patients attend the hospital clinic throughout pregnancy.

An emergency outdoor service is provided by the hospital for the domiciliary treatment of acutely ill patients (chiefly because of haemorrhage) at the request of practitioner or midwife.

The total deliveries were 2,677 (booked 2,479, unbooked 198) and there were 15 abortions.

There was 1 maternal death = 0.36 per 1,000 live and stillbirths. The stillbirth rate was 27.2 per 1,000 live and stillbirths (15.4 excluding malformations incompatible with life). The neonatal death rate was 30.6. The forceps rate was 5 per cent and the Caesarean section rate 2.4 per cent.

The only maternal death occurred in a 10-para with a breech presentation and hydramnios. There was no toxaemia. One hour after external version and high rupture of the membranes pains started. Twenty-eight hours later there was antepartum bleeding (about 10 ounces) and two hours later a stillborn child, weighing 7 pounds, was delivered. The total blood loss was about 60 ounces. Uncontrollable bleeding continued, necessitating subtotal hysterectomy. At the postmortem thrombosis of both ovarian veins, with an old white clot in the ieft vein, was found. There was necrosis of the anterior half of the pituitary.

This is an admirable record of a service in which the control is dispersed but where this dispersion is checked by efficient organization. J. Y.

NOTICE

ASSISES FRANCAISES DE GYNÉCOLOGIE

PARIS, 21–24 Juillet 1954

Les prochaines **ASSISES FRANCAISES DE GYNÉCOLOGIE** se tiendront à Paris, du 22 au 24 Juillet 1954, sous la Présidence de **M. le Dr Claude BECLÈRE** (de Paris).

M. le Professeur Rodriguez LOPEZ, de Montevideo (Uruguay), Membre d'honneur de la Société Française de Gynécologie, a bien voulu en accepter la Présidence d'honneur.

Question a l'ordre du jour:

LE TRAITEMENT DES PROLAPSUS GÉNITAUX

Rapporteur Général : **M. le Dr Raoul PALMER,** de Paris.

M. le Professeur BARON, de Dijon, présidera le Comité local d'organisation.

Un certain nombre de festivités sont prévues pour agrémenter cette réunion.

Pour tous renseignements et inscriptions:

S'adresser à **M. le Docteur R. SENECHAL,** 31, rue Raynouard, PARIS-16e Secrétaire général de la SOCIÉTÉ FRANCAISE DE GYNÉCOLOGIE.

BOOK REVIEWS

"Understanding Natural Childbirth." By H. THOMS and L. G. ROTH. Staples Press, Ltd., London, 1952. Pp. 192; illustrated; price 17*s.* 6*d.*

IN this day and age there is a growing public demand by the mother-to-be for a better understanding of the mysteries of childbirth. The ideas of Grantley Dick Read are gaining ever-widening acceptance, and are in use in one form or another in many hospitals and by many obstetricians. This little book by well-known authors is intended for the pregnant woman who wishes to know what to expect when she has her baby, and how she herself can best assist in procuring a normal confinement. In just over 100 pages the elements of the physiology and anatomy of childbirth are simply described, and the system of antenatal instruction is explained, aided considerably by a series of excellent photographs. The reviewer would doubt, however, the advisability of introducing parties of expectant fathers and mothers, unmasked and ungowned, into the delivery room, and it is disappointing that no attention is paid during the antenatal period to the importance of breast feeding as a process beneficial to mother and child.

In all other respects, however, the book is admirable and can be recommended as very suitable reading for women who want to understand what will happen when they know they are pregnant.

"Nurse's Handbook of Obstetrics." By LOUISE ZABRISKIE and N. J. EASTMAN. Ninth edition. J. B. Lippincott Co., Philadelphia and London, 1953. Pp. 695, illustrations 377; price 40*s.*

THIS well-known American book of obstetrics must surely be one of the most comprehensive of its type. The authors, possessing as they do an unusual insight into the ever widening knowledge required by nurses, have literally filled the book from cover to cover with information, and in this new edition the material has been revised and thoroughly modernized. The emphasis on the prevention of prematurity, and on the emotional aspects of pregnancy, for instance, throw into focus the trends of present-day obstetrics.

It is difficult to compare the training of the American obstetric nurse with that of the British midwife, as their functions and therefore their needs are so very different. It is nevertheless disappointing that in dealing with the subject of placenta praevia, for example, the instructions as to the role of the nurse are so little clarified as to detail. The use of oxygen is not mentioned, nor is the recording of the foetal heart rate; the same criticism can be advanced of the management of prolapse of the cord, and of post partum haemorrhage—a triad of obstetric emergencies in which the nurse must act effectively before the doctor can hope to arrive.

The liberal use of diagrams and photographs is one of the many attractive features of this book, and adds considerably to its value.

The "Situation Questions" at the end of each section provide an easy (perhaps too easy) method of testing the reader's acquisition of knowledge, and are viewed by the staid reviewer with misgiving. Their use will perhaps give an over-optimistic estimate of facts truly assimilated.

The book is excellently produced, and makes most interesting reading. For the British midwife, however, it is best used to extend the theoretical background to the eminently practical training for which she is renowned the world over.

"A Guide to Obstetrics in General Practice." By WILLIAM C. W. NIXON, M.D., F.R.C.S., F.R.C.O.G., and ERIC B. HICKSON, M.R.C.S., L.R.C.P., D.R.C.O.G. Staples Press, London, 1953. Pp. 301; illustrations 35; price 30*s.*

THIS book presents the wealth of experience of the authors in both hospital and domiciliary practice. It is far more than a guide to obstetrics in general practice, it is a contribution to obstetrics that will be welcomed by the obstetrician, the general practitioner, the student, and midwife alike. The contents of the book have been based on (1) obstetric subjects which have appeared in the series "Any Questions", in the *British Medical Journal* during the past 5 years; (2) an analysis of the midwives' calls for medical aid in the county of Wiltshire for the years 1944 to 1946; (3) the work of the obstetric Unit, University College Hospital, London; (4) personal records and experience of one of the authors in a semi-rural practice for 25 years.

Dr. Harold Waller has contributed chapters on breast-feeding, the care of the premature baby, and disorders of the newborn, and Dr. Sheila G. Ransom gives a very well-balanced appraisal of modern analgesics and anaesthetics. The emotional aspects of pregnancy and labour have been presented in some detail by Dr. Elizabeth Tylden.

The descriptions of the minor operative procedures are very well set out, together with appendices giving details of the contents of the obstetric bag, the procedure to be followed in child adoption, in notification

of the birth and in other circumstances that must arise from day to day in general obstetric practice.

The whole book is very readable and there is no doubt that it will prove very popular, and the authors and their collaborators are to be congratulated on its production.

"Aids to Gynaecology." By W. R. WINTERTON. Eleventh edition. Baillière, Tindall & Cox, London. Pp. viii + 196; illustrations 15; price 6s.

THIS 1953 edition of one of the popular "Aids" series has been largely rewritten by a gynaecologist of extensive practical experience. For a book of such modest size the wide range of material has been admirably dealt with, and the style is scholarly, without being dull.

The author has contrived to present both sides of most of the important controversies, and tactfully states his own preference, a point of considerable importance to the student. Apart from the theory, most of which is entirely up to date, Mr. Winterton has drawn on his own extensive experience to give much valuable advice not often found in books of this size.

Many authorities would not perhaps agree with the author's insistence on the relationship between urethrocele and stress incontinence and, considering how much ground has been covered, it might have been possible to include a differentiation between urge incontinence and stress incontinence. The pressing necessity for brevity has occasionally caused statements which verge on the enigmatic, but in general the work could serve as a lesson in lucidity to the writers of more pretentious volumes.

To the reviewer, unfamiliar with the "Aids" series, the book has been an agreeable surprise, and it is recommended without reservation to both students and practitioners.

"Proceedings of Symposia on Exfoliative Cytology, Cancer Detection and Diagnosis." Edited by H. E. NIEBURGS, M.D. Medical College of Georgia, Augusta, Ga., March 1953. Pp. 48.

THIS typewritten paper-covered little volume is a collection of 22 abstracts by well and less well known authors and presents a rather hotch-potch collection of papers on cancer, covering fact and fancy alike.

The British reader will be surprised to find that one author (John E. Dunn) predicts not only a cancer screening campaign for the entire female population of the U.S.A., but also expects to eliminate invasive cervical carcinoma completely since the disease will be recognized by exfoliative cytology and cured at the pre-invasive stage.

Other articles include subjects not accounted for in the title of this volume, e.g., a rather controversial series of papers on cancer genesis (uterine), endocrine factors in carcinoma of the pelvis and breast and an excellent paper by Stephen W. Brown on the Clinical Application of Radio-active Isotopes.

The reader who has been optimistic enough to work his way through these 22 articles will feel disappointed when he comes to the end. The reviewer personally doubts whether the diligent student after reading these abstracts will in general be better acquainted with the various problems discussed. There are no illustrations.

"Annual Report on the Results of Treatment in Carcinoma of the Uterus." Eighth volume: Statement of Results Obtained in 1946 and Previous Years (collated in 1952). Editorial Office: Radiumhemmet, Stockholm 60. 1953.

YEAR by year the scope of these Reports has been gradually widened. Whereas the first 5 Reports deal strictly with the results obtained by radiotherapy in patients with cervical cancers, the 6th Report also contains an evaluation of surgical treatment in cervical carcinomata, the 7th Report includes statements on Stage 0 carcinoma of the cervix, and the present 8th volume has extended the scope even further to include carcinoma of the corpus, carcinoma of the corpus and endocervix, as well as of the corpus and ovary, and pelvic cancer.

The number of contributors is steadily on the increase, 8 additional institutions having joined the 61 contributors to the 7th Report; thus the present Report contains statements from 69 institutions in 15 different countries and covers a total of 83,291 cases of uterine carcinoma.

The information submitted by the individual collaborator is presented in combined tables including figures from all collaborators. Three different series of combined tables are given:

Series I, relating to the entire period on which the individual institutions had reported.

Series II, relating to the years 1942 to 1946.

Series III, relating to the latest year.

Evaluating the tabulated results obtained in carcinoma of the cervix 5 years after the beginning of treatment, the reader is struck by the steady improvement in recovery rate. The over-all relative apparent recovery rate of 34.1 per cent in this Report is the highest yet presented in this series; the corresponding figures for 1937 being 26.3 per cent; for 1938, 27.6 per cent; for 1940, 26.7 per cent; for 1948, 30.9 per cent; for 1950, 31.8 per cent; and for 1951, 32.6 per cent. Studying the results of the latest 5 years only, the over-all apparent recovery rate in cervical cancer rose from 36 per cent in 1951 to 36.9 per cent in 1952 and 38 per cent in the present Report. The variation in these three series does not seem to have been materially influenced by the increased number of cases presented by the new collaborators, but is due both

to a reduced proportion of advanced cases and to an increased apparent recovery rate in all stages. The improvement in recovery rate between the present analysis and the previous year is remarkable in so far as during this year no marked change in the methods of treatment employed has occurred.

Results of primary surgical treatment of cervical carcinoma were studied in Volume 7. A similar study in the present Report confirms the conclusion that the use of primary hysterectomy in selected cases does not necessarily improve the results obtainable by adequate radiotherapy.

Therapeutic results on carcinoma of the corpus uteri were submitted by 12 collaborators on a total of 3,857 cases, of whom 3,745 were treated. The 5-year absolute apparent recovery rate is 50.9 per cent. As the material presented is small, no definite conclusions can be drawn. The preliminary impression, however, is that there is no significant difference in recovery rate between primary hysterectomy and primary radiotherapy. Analysis of the available material showed further that there is no difference in the stability of the calculated recovery rates in carcinoma of the corpus and cervix. The fact that the over-all relative apparent recovery rate in corpus carcinoma is higher than in cervical cancer corresponds with general experience.

Figures relating to carcinoma *corporis et endocervicis*, carcinoma *uteri et ovarii*, and carcinoma pelvis have been submitted by 9 collaborators. Carcinoma pelvis is the smallest of the 3 groups. The largest and most interesting group comprises cases of carcinoma *corporis et endocervicis*. The available material, however, is insufficient to decide whether these cases should be kept separate or included with the cervix or corpus groups.

E. Wachtel

14TH BRITISH CONGRESS OF OBSTETRICS AND GYNAECOLOGY

PRELIMINARY NOTICE

The above Congress will be held at Oxford on 27th, 28th, 29th and 30th July, 1955.

Subjects already selected for Discussion are:

1. The Rôle of the Qualified Midwife, the Family Practitioner and the Obstetric Specialist in the Conduct of Normal Labour.
2. The Aetiology, Prevention and Treatment of Pre-eclamptic Toxaemia of Pregnancy.

Gynaecological subjects will be announced later.

All communications relating to this Congress should be addressed to the Secretary, 14th British Congress, Maternity Department, Radcliffe Infirmary, Oxford.

REVIEW OF CURRENT LITERATURE

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ANATOMY AND PHYSIOLOGY

164. **Variations in Size of Vaginal Epithelial Cells Dependent on Age and Other Factors during Human Life.** (Citometria delle cellule epiteliali superficiali della vagina umana e sue variazioni in rapporto all'eta ed ai diversi momenti della vita sessuale.)

By M. Franceschini. *Minerva Ginec.*, **5**, 205–217. Mar. 1953. 39 refs. 12 figs. 1 table.

Following up work done on the superficial measurements of cells facing the lumen of the vagina in *mus decumanus* under different age and hormonic conditions, the author has examined similar epithelial mosaics obtained from the human female. Material for measurement is obtained by applications of silver nitrate as described in the author's work on *mus*.

The research shows that there is a very great difference in superficial area of the cells in question depending on the concentration of oestrin in the blood and tissues. Certain differences in the shape and axis of the cells was also noted.

In the foetus about the middle of the ninth month, the area of such cells, expressed in μ^2 averages 130, rising at birth to 563 and falling to 182 and 117 at 11 and 25 days after birth. During the normal menstrual cycle, the measurements at the 4th, 10th and 14th days are 573, 728 and 1122 respectively, falling again rapidly after ovulation to 359 on the 18th day. During pregnancy, values found were μ^2 869 at the 2nd month, 1304 at the 5th, whilst the maximum size found was 1688 at the 8th month, falling to 414 by the 4th day of puerperium.

One year after the menopause the size was 364; after 20 years it was down to 107. A year after ovariectomy a value of 199 was found. The smallest measurement of all was 74 found in a case diagnosed as hypo-oestrinism with virilism. This is in contrast with 1282 where cystic hyperplasia of the endometrium was present in a woman of 41 suffering from menorrhagia. *W. C. Spackman*

165. **Action of the Ovarian Hormones on Uterine Muscle.**

By G. W. Corner and A. Csapo. *Brit. Med. J.* **1**, 687–693. Mar. 28, 1953. 48 refs. 5 figs.

The authors review the research on the relationship between the ovary and the behaviour of the uterine muscle, starting with the discovery in 1907 by Dale and Cushny that pregnancy causes reversal of the normal uterine response to stimuli.

Analysis at the level of the muscle cell has shown that contraction can be produced in vitro by bringing together the constituents of the process—namely, the protein complex actomyosin (A.M.) the energy-rich adenosine triphosphate (A.T.P.) and ions. The final contractile substance is A.M., the concentration of which is constant in skeletal muscle but in uterine muscle varies with the different hormonal conditions of the ovary, rising in pregnancy and falling with castration. Ovariectomized rabbits showed a great decrease in A.M. concentration, the process being reversed on supplying them with oestrogen. Progesterone had no such effect.

The relation of the ovarian homones to A.T.P. was

also studied. A low oestrogen level was accompanied by a low A.T.P. concentration, and the increase in response to oestrogen administration was much quicker than that of A.M., possibly indicating that A.T.P. is involved in the resynthesis of the contractile proteins. Oestrogens also selectively increase the glycogen content of the myometrium but not of skeletal muscle. Progesterone has no effect in increasing the A.T.P. concentration or the glycogen content of the uterus.

The authors observed the relation between A.M. concentration in the myometrium and the working capacity of the muscle, by measuring the isometric tension, that is, the force developed by contraction of an electrically stimulated strip of muscle that is not allowed to shorten. Experiments showed that maximum isometric tension depended on A.M. concentration. Castration caused a fall in both, which could be restored by oestrogen administration. Progesterone affected neither. It is probable that the ovarian hormones act not at the molecular but at the cellular level, by producing favourable or unfavourable conditions for the reactions taking place in the cell. The authors' experiments indicate that they act by altering the potassium balance of the cells. If stimuli are applied at a constant frequency, the oestrogen-dominated uterus shows an effect similar to that of the frog-heart staircase, while the progesterone-dominated uterus shows a staircase sloping in the reverse direction, called by the authors a "negative staircase." Intermediate slopes are produced by varying the proportions of the two hormones administered simultaneously. The positive staircase disappears at a low temperature, while the slope increases with a rising temperature. The negative slope decreases with increasing temperature.

If the potassium-sodium ratio in the bath is lowered, the oestrogen uterus shows an increase of tension within 2 minutes, but the slope of the staircase is only slightly reduced. If the tissue is washed in potassium-free Krebs solution for 2 hours the staircase gradually disappears, with a corresponding decrease in tension. If the potassium-sodium ratio is then suddenly increased by changing to normal Krebs solution, the tension drops and remains there for 20 minutes, then increases slowly. In other words, for a short time a negative slope appears, the oestrogen uterus behaving like the progesterone uterus. On the other hand, in the progesterone uterus aa increase of either temperature or potassium-sodium ratio causes a gradual disappearance of the negative staircase. If the ratio is high enough a slight positive slope appears, resembling that of the oestrogen uterus. Thus it is shown that, by altering the potassium concentration of the perfusion fluid, the normal staircase behaviour of the uterus can be reversed. Maximum tension too is affected by changes in the potassium-sodium ratio, the oestrogen uterus showing a decrease in tension with a high ratio, while the progesterone uterus shows an increase.

From these experiments the authors conclude that oestrogen and progesterone have opposite effects on myometrial function and that these effects can be counteracted or even reversed by changing the temperature or the extracellular potassium concentration. They consider it possible that the ovarian hormones, by altering the potassium balance of the myometrium, may modify the activity of certain enzyme systems involved in muscle cell action.

A.T.P. and other phosphates have been shown to play an important part in muscle function not only because of their high energy content but also because of their high-valency negative charges which link cations, especially potassium, to the contractile proteins. Their concentration therefore determines the resting potential of the cell. Thus a change in the myometrial potassium balance caused by the ovarian hormones could modify a series of intracellular reactions and so produce great variations in the function of the uterus as a whole.

This theory, the authors consider, may ultimately explain pregnancy reversal and other problems of uterine physiological and hormonal action.

Kathleen Bower

166. Does Menstrual Blood Contain a Specific Toxin?

By B. ZONDEK. *Amer. J. Obstet. Gynec.*, **65**, 1065–1068. May 1953. 8 refs.

It has long been supposed that menstrual blood contained a toxin and the writings of Smith and Smith of Boston, U.S.A., have furnished important support for this view. They found that it contained a toxin so potent that subcutaneous injection of 0.05 to 0.2 ml. of whole menstrual discharge would kill 95 per cent of 19- to 24-day old rats within 48 hours. This seemed to be confirmed by the observation that 50 to 100 mg. of fresh endometrium got from the uterus during menstruation was lethal to rats whereas 200 to 300 mg. taken at other times was non-toxic. Smith and Smith concluded that the toxin was identical with necrosin, the material that Henkin found in the pleural exudate of dogs following the inflammatory reaction caused by turpentine and think that it is the precipitating cause of toxaemia as well as menstruation.

Zondek has been unable to confirm these conclusions. He collected the menstrual blood under relatively sterile conditions by introducing a sterile vaginal speculum (tube) at the onset of menstruation and collecting blood for 1 to 3 hours. The death rate in injected rats was only 5 per cent and was no greater than after injection of other tissue extracts. The rats that died were found to have a bacteraemia, the organisms being identical with those cultured from the original menstrual material. Death could be prevented by injecting penicillin and streptomycin 1 hour before the injection of menstrual blood.

F. J. Browne

PREGNANCY

167. Symposium on Ante-Natal Care.

By G. W. THEOBALD, A. P. BARRY, and M. K. CUSACK. *J. Irish med. Ass.*, **33**, 28–35. Aug. 1953.

Mr. Theobald suggests that a practitioner ought to

set aside a special session for his antenatal patients so that all routine procedures can be carried out satisfactorily. Emphasis should not be placed upon the mechanical factors associated with pregnancy and labour, and it is pointed out that most of the conditions which cause trouble operate long before the 36th week of pregnancy. The author believes that the doctor can be of the greatest service to the expectant mother between the 28th and 30th weeks of pregnancy.

At the first visit to the antenatal clinic the patient should be examined very thoroughly and an estimation of the haemoglobin level made by the Talquist method. Mr. Theobald finds this method to be accurate to within 10 per cent. If the patient has had pregnancies previously then her past obstetric history is considered the best guide to her behaviour in the present pregnancy. The author does not subscribe to the view that external pelvic measurements are of little value and states that if the interspinous diameter is 26 to 28 cm., the intercristal 25 cm. and the external conjugate 18 to 20 cm., there is little likelihood of cephalo-pelvic disproportion. Patients under 5 feet 2 inches in height are more liable to experience trouble in delivering themselves.

Mr. Theobald does not believe in stripping the patient for examination again until the 30th week; at this stage in pregnancy the doctor must be on the lookout for (1) multiple pregnancy, (2) hydramnios and (3) breech presentation. At the 36th week, in primigravidae, a pelvic assessment should be made by vaginal examination.

Consideration of the pregnancy toxaemias is deliberately left to the end of the article. Whereas there is no need to carry out an abdominal examination at each visit the author stresses the importance of doing the following four things each time she attends the doctor:—

(1) Take her blood pressure.
(2) Examine her urine.
(3) Weigh her.
(4) Look for oedema.

Every antenatal patient should attend her doctor once per fortnight until the 34th week and then each week. Not more than 1 pound in weight per week should be put on during the first 6 months and during the last 3 months it is desirable that there should be little gain in weight. Any rise in blood pressure, albuminuria, or sudden increase in weight, demands immediate treatment.

Such troublesome complaints as leucorrhoea and pruritus, varicose veins, haemorrhoids, morning sickness, cramps, heartburn and sleeplessness are discussed briefly and the author concludes by listing the types of case which he thinks ought to be referred for delivery to a well equipped maternity hospital.

Dr. Barry supports Mr. Theobald's suggestion that the practitioner ought to hold a special session for antenatal patients and deprecates frequent abdominal examination during the first 7 months of pregnancy. This author emphasizes the poor physical condition of many pregnant patients in Ireland.

Careful antenatal preparation of the breasts is advised, in the belief that this will result in successful breast feeding with a greatly reduced risk of infection. The author is in favour of stripping the breasts of colostrum during the last 6 weeks of pregnancy.

Dr. Barry is strongly against the routine use of X-ray pelvimetry in primigravidae on the grounds that it exposes the foetal gonads unnecessarily to the effects of radiation. It is, in his opinion, a useful supplement to clinical pelvimetry. The author concludes by discussing briefly the management of pyelitis and leucorrhoea in pregnancy. His treatment of these conditions is along accepted lines.

Dr. Cusack points out that in Ireland, outside the few cities and larger towns, antenatal care is largely in the hands of practitioners. The suggestion by Mr. Theobald that all antenatal patients should be seen fortnightly, is unfortunately considered to be unpractical as the patients simply would not attend. Because of the state of the blood transfusion service in Ireland today, the author does not believe that routine blood grouping and Rh testing in pregnant women is justifiable. Weighing of patients at the antenatal clinic is, in the author's opinion, the least valuable of the procedures carried out at the clinic, as an abnormal increase in weight frequently does not herald any untoward development. Routine W.R. testing is considered to be unnecessary. Dr. Cusack, speaking as a general practitioner, does not believe in the importance of routine haemoglobin estimations; iron in some form should be given to all pregnant women and those who are anaemic will improve rapidly.

J. K. Russell

168. **Association between Period of Gestation and Length of Menstrual Cycle.**

By T. McKeown, J. R. Gibson, and T Dougray. *Brit. med. J.*, **2**, 253–255, Aug. 1, 1953. 16 refs. 5 figs.

The authors, from the Department of Social Medicine, University of Birmingham, and St. Chad's Hospital, Birmingham, have investigated the association between the period of gestation and the length of the menstrual cycle in 716 women with regular cycles, and in whom the data were considered adequate. Mothers were given a calendar to record each day of bleeding during the year after the birth of the child. Only those mothers of single births whose children survived to the end of the first year are included—this to exclude abnormal foetuses which might have influenced the duration of gestation.

The mean length of cycle for each woman was calculated after excluding cycles whose lengths were judged inconsistent with the other observations. The adjusted means were charted to relate to the mean period of amenorrhoea. This indicated that the period of amenorrhoea increases by about one day for each additional day in the length of the cycle. The authors conclude that variation in the period of amenorrhoea according to the length of the menstrual cycle is probably determined by variation in the interval between the onset of menstruation and ovulation; and that the period between ovulation and birth—approximately 266 days—is independent of the length of the cycle.

Eileen Wilson

169. **Detection of Weak Rh Antibodies in Maternal Antenatal Sera—The Value of Enzyme-treated Test Cells.**

By F. STRATTON. *Lancet*, **1**, 1169–1172, June 13, 1953. 9 refs. 3 tables.

The author points out the importance of knowing in advance of labour whether or not Rh antibodies are present in the maternal serum. The technical details of testing for Rh antibodies using enzyme-treated red blood cells (papainised cells) are described. From comparisons made the author claims that this test gives positive results at a higher dilution than the Coombs test or agglutination tests in saline or albumen. The test is made on a slide at room temperature and at 37° C, and it is claimed as a suitable test for screening purposes.

H. H. Fouracre Barns

170. **Hæmoglobin and Red Cells in the Human Foetus and their Relation to the Oxygen Content of the Blood in the Vessels of the Umbilical Cord.**

By J. WALKER and E. D. N. TURNBULL, *Lancet*, **2**, 312–318, Aug. 15, 1953. 10 figs. 19 refs.

The authors are to be congratulated on the production of this important paper. They have investigated the haemoglobin level, red-cell count and oxygen content of the umbilical cord blood at different stages of human pregnancy. The study in early pregnancy was made of foetuses obtained from terminated pregnancies. Very few normal cases were available for study between the 22nd and 36th week of pregnancy.

In normal pregnancy it was found that the mean haemoglobin level rose steadily from 9 grams per 100 ml. at the 10th week to 14–15 grams per 100 ml. by the 22nd–24th week. From the 36th week there was a rise from 14–15 grams to 16.5 grams per 100 ml. at the 40th week and to 18.8 grams at the 43rd week. The mean red-cell count rose from 1,420,000 per c.mm. at the 10th week to 3,280,000 at the 25th week. By the 40th week the count was 4,350,000 and reached to 4,830,000 at the 43rd week. Investigation of the oxygen content of the umbilical vein blood showed a decrease from 12.5–14 vols. per cent at 20–22 weeks to 10.8–12.7 vols. per cent at 39–40 weeks and 7.8–9.7 vols per cent at 42 weeks. The percentage saturation with oxygen was also found to fall as pregnancy advanced.

In pregnancies complicated by severe pre-eclamptic toxaemia, threatened abortion and intra-partum foetal distress, the haemoglobin levels and red-cell counts were abnormally high as compared with those of the normal pregnancy of the same duration. The oxygen content and the percentage saturation with oxygen of the umbilical vein blood was lower than normal in cases of pre-eclamptic toxaemia.

The authors suggest that the rise in the haemoglobin level and increase in the number of red cells seen in late pregnancies is a response of the foetus to a falling oxygen supply as pregnancy advances. They also suggest that one of the effects of pre-eclampsia and threatened abortion is to interfere with the oxygen supply of the foetus and so produce the abnormally high haemoglobin level and red-cell count in late pregnancy. In a few cases of placenta praevia examined the blood levels were normal. They suggest that the explanation for this finding is that the bleeding is due to a mechanical separation of a small area of placenta and not to any functional defect of the placenta as a whole. [It seems possible that the interval between the bleeding and delivery is not long enough to cause the blood changes in the foetus.]

They point out that intra-partum foetal distress may be caused by acute conditions such as maternal anoxia, prolapse of the cord, etc. Yet they found that the blood levels were abnormally high in the cases of foetal distress investigated. They conclude that foetal distress is uncommon in normal pregnancy except in the acute circumstances mentioned above, and that when a foetus shows distress during labour it has probably suffered from a degree of oxygen lack for some time before labour. *H. H. Fouracre Barns*

171 **Cytology of Amniotic Fluid.** (Sulla citologia del liquido amniotico.)

By I. SILIOTTI. *Riv. Obstet. Ginec. prat.*, **35**, 217–233, May 1953. 3 figs. 10 refs.

The writer gives the relative incidence and describes the morphology of the various cells in amniotic fluid at the end of pregnancy. Epithelial cells, amniotic and foetal, outnumber the rest by more than 4:1. The size, shape and colour of all the cells is not remarkable with one possible exception. This is the presence, when the foetus is female, of a basophilic net in the cytoplasm of some navicular epithelial cells. All other epithelial cells, navicular, cuboidal and polygonal, are acidophilic. The author believes that the basophilic epithelial cells are specific and speculates about antenatal determination of sex. The number of specimens examined is not given. *M. Caturani*

172. **Complications Associated with High Multiparity : A Clinical Study of 518 Cases.**

By J. K. FEENEY. *J. Irish med. Ass.*, **32**, 36–55, Feb. 1953.

In the author's opinion a grand multipara is one in her eighth or later pregnancy. In the Coombe Lying-in Hospital during the years 1950 and 1951, 518 such patients were delivered—12.6 per cent of all deliveries.

Details are given of the age groups and parity of these patients and an analysis is made of the stillbirths and neonatal deaths which occurred in the group. Excluding abortions and adding 16 extra twin foetuses, 465 viable babies were born. There were 37 stillbirths and 41 neonatal deaths—a total loss of 73 or 16.7 per cent. This rate was found to be about twice the rate for all other mothers in the hospital. The author found that such factors as malnutrition, increased incidence of hypertension, accidental haemorrhage, prematurity and prolapse of the cord were, in large measure, responsible for the difference. The incidence of congenital deformity as a cause of foetal death, was not as high in grand multiparae as in other patients.

There were 5 maternal deaths in this series and these are discussed in detail. Three were associated

with toxic accidental haemorrhage, 1 with eclampsia and 1 with non-toxic accidental haemorrhage. This represents a maternal death rate of 10 per 1000 and over the same period the maternal death rate for 7,214 patients delivered in the hospital, or on the district served by the hospital, was 1.5 per 1000.

It is suggested that placenta praevia in multiparae should be treated with special care. In the author's experience placenta praevia is particularly liable to cause heavy bleeding when associated with multiparity. The author prefers the lower segment type of operation in cases of placenta praevia and a number of points of technique are detailed, in the belief that they may be helpful in the reduction of bleeding during operative delivery.

The frequency of anaemia causes much anxiety at the Coombe Lying-in Hospital. Thirty per cent of all obstetrical patients had a haemoglobin level below 50 per cent. There are a number of reasons for this wide-spread anaemia and among the more important are malnutrition, faulty diet habits, lack of cooking facilities in tenement houses, anorexia and vomiting, focal sepsis and multiparity.

The incidence of breech presentation among the grand multiparae was found to be twice as high as among all other patients (7.1 per cent and 3 to 4 per cent). Oblique and transverse lie, presentation and prolapse of the cord were also found to occur more frequently among these patients.

Fourteen cases of disproportion in grand multiparae are described in detail and the author stresses his belief that obstetrical tragedies for mother and foetus may be avoided if the obstetrician remembers that disproportion may well occur in these patients. Nine Caesarean sections and 1 Caesarean hysterectomy were done on these 14 patients. Three of the 14 babies were lost but all the mothers survived. The Caesarean hysterectomy was carried out on a patient with ruptured uterus.

The incidence of post-partum haemorrhage, rupture of the uterus and retention of the placenta was found to be higher in the grand multiparae.

In the 518 cases studied there were 6 cases of rupture of the uterus—1 patient died. Eleven Caesarean sections and 9 Caesarean hysterectomies were performed and the details of these cases are given.

The article concludes with a series of suggested precautionary measures which should be applied in dealing with grand multiparae. Attention paid to these points would reduce the risks to mothers and babies. *J. K. Russell*

173. **A Report on Eclampsia in New Zealand for 1952.**

By the Obstetrical Research Committee of the Medical Research Council of New Zealand. *N.Z. med. J.* **52**, 198–199, June, 1953.

Eighty-eight cases of eclampsia occurred in 52,886 births (1.55 per mille). There were 3 maternal deaths (3.66 per cent) and 16 infant deaths (17.6 per cent). 48 cases were regarded as very mild (less than 3 fits and mother and infant surviving).

Ante-partum eclampsia occurred 25 times, intra-partum 29 times and post-partum 28 times. Most of the latter cases were mild. *L. Woodrow Cox*

174. **Treatment of Toxæmia of Late Pregnancy with Hydergin.** (Über die Behandlung der Gestose mit Hydergin.)

By F. Rupp. *Gynaecologia, Basle*, **135**, 390–404, June, 1953. 1 fig. 55 refs.

Between June 1949 and June 1950, 60 cases of toxaemia of late pregnancy were treated with Hydergin. Twenty cases were treated by oral administration, 2 by parenteral administration and 38 by combined treatment.

The dosage was 5 to 10 drops of oral solution 3 times a day. By injection 0.1 to 0.3 mg. were given up to a maximum of 2.1 mg. per day. Combined treatment consisted in 5 to 20 drops (5 mg.) by mouth and 1.8 mg. by injection. Intravenous drip was also used, giving 0.3 mg. per hour in normal saline.

In 47 cases treated during pregnancy, 44 were cured and 3 improved. In 9 patients with pre-existing renal or essential hypertension, 4 were cured and 3 improved, while 2 remained unchanged. It is claimed that treatment with hydergin causes a more rapid return of the blood pressure and urine to normal after delivery. No ill effects were noted on mothers or children. *Josephine Barnes*

175. **The Present Treatment of Post-abortive Tetanus.** (A propos du traitement actuel du tetanos post-abortum.)

By Henrion. *Bull Féd. Soc. Gynéc. Obstét.*, **5**, 103–109, 1953. 48 refs.

Having reviewed the question of post-abortive tetanus the writer is convinced that the prognosis in this terrible disease which still kills 8 out of 10 patients can be improved if attention is primarily paid to avoiding the complications which cause death rather than continuing to rely on the active treatment by means of illusive specific anti-infection therapy.

A case of a pregnant woman of the age of 24 is described in which retained products were removed when she was only 8 weeks pregnant and in whom there had been slight temperature. Twenty-four hours later the patient had slight trismus with a normal pulse and no temperature. Treatment comprised anti-tetanic serum, anatoxin, penicillin, chloral, Flaxedil, cardiac tonics, intravenous glucose and fluid by a small stomach tube. Death came suddenly, and post-mortem was refused.

Methods of treatment are discussed.

(1) *Serum.* Abel's work on monkeys is alluded to. The less the delay the better; if there is undue delay in giving of serum, then no matter what dose is given, the patient may succumb. Clinically as the dose of toxin present is unknown, a very large dose of anti-toxin, as soon as diagnosis is made, is recommended. Abel advised 80,000 International units as being sufficient to neutralize all free toxin and he recommended the injection of a further 10,000 International units daily for 4 or 5 days. In general it is pointed out that intrathecal injections of the serum do not pro-

duce any better results than by other routes except in the opinion of Gold.

(2) *Penicillin.* It is definitely active against the tetanus bacillus. Eight writers are mentioned who found their results improved with this antibiotic and only one writer who did not do so.

(3) *Hysterectomy.* While the organisms are localized in the uterus it would appear justified. Animal experiments reveal that, in those cases with symptoms of tetanus, the organisms have often penetrated far beyond the uterus. It was thought that the toxin was transported by nerve filaments but Firor and Pelloia have shown it is carried in the blood and lymph. Up to several years ago in France it was morally essential to perform hysterectomy and in several countries it is still done systematically.

Quenu and Bauchart have published the following figures:

93 deaths in 116 cases where total hysterectomy was carried out—83 per cent.

30 deaths in 40 cases where curettage only was done—75 per cent.

68 deaths in 101 cases where there was no surgical intervention—67 per cent.

Moreover total hysterectomy gives 90 per cent mortality and sub-total 56 per cent. Hysterectomy is ruthlessly condemned—gentle removal of retained products is advised with injection of penicillin into the uterine cavity and cervix.

(4) *Sedatives and narcotics.* Barbiturates, chloral, avertin all can calm the patient and bring about a certain muscular relaxation but they cannot prevent tetanic seizures. Their action is essentially central, while the toxin is acting at the neuromuscular synapse. The writer indicates that the less these are used the better.

(5) *The relaxants and curare series.* Curare appears to be a real antidote as it acts at the right place. Cole's work in 1934 is alluded to. Flaxedil is considered one of the best preparations—and myanesin was also satisfactory. As large a dose as 80 mg. of Flaxedil was used on one occasion and this caused the trismus practically to disappear but at the same time the swallowing reflex tended to disappear causing choking. It was finally considered not desirable to run the risk of inhalation pneumonia and to give smaller frequent doses. The advantage of myanesin is that it can be given by mouth. A small plastic indwelling stomach tube was found much less irritating than a rubber one.

(6) *Tracheotomy and the poliomyelitis respirator.* Pulmonary complications and respiratory failure account for a very large number of deaths from tetanus. Respiratory failure is the result of intoxication of the central bulbar centres. If respiration is difficult there should be no hesitation in doing a tracheotomy. It is essential to do this before irreversible cardio-pulmonary changes have occurred. This procedure allows easy oxygenation, avoids anoxaemia, pulmonary atelectasis and respiratory fatigue. The tracheotomy is performed at the level of the second or third ring of the trachea under general anaesthesia with infiltration.

Finally it is essential to make use of the poliomyelitis respirator. If any patient with tetanus gets respiratory failure there is only one method of saving them and that is the "iron lung." *D. Maxwell*

176. Acute Pulmonary Edema in Pregnancy, with Report of a Case responding to New Form of Therapy.

By M. A. GOLDMANN and N. P. PRIMIANO. *Amer. J. Obstet. Gynec.*, **65**, 314–319, Feb. 1953. 21 refs.

Acute pulmonary oedema may occur at any period of gestation from conception to the post-partum period. Approximately 56 per cent occur during labour and in the 24 hours immediately following. There is an apparent but inadequately documented increased incidence in toxaemic patients and there is also an apparent slight increase in heart disease, but cases have been reported in which neither of these conditions was present. It may be associated with various lesions of the lungs, tracheo-bronchial tree and the central nervous system, as well as of the heart. Any factors leading to high pressure in the pulmonary circulation or dilatation or increased permeability of the pulmonary capillaries may precipitate an attack. Physiological changes in pregnancy that favour its occurrence are (1) increase of plasma volume, (2) relative decrease of plasma proteins, (3) increased cardiac work (increased venous return and cardiac output). In the presence of toxaemia the additional burden of hypertension on the heart and increased capillary permeability may be added.

The authors report a case in a pregnant patient (15-gravida aged 43 years) who had very severe hypertension at term. Shortly after admission the membranes ruptured spontaneously; vaginal examination revealed a cephalic presentation, head floating and cervix not dilated. While lying supine on the examination table she complained of flushing and a choking sensation. She became severely dyspnoeic and cyanotic and developed acute pulmonary oedema of the greatest severity. She was given oxygen under positive pressure, morphine sulphate, aminophylline atropine, sodium amytal and digalen successively without benefit. Administration of alcohol vapour (ethanol-oxygen vapour) was then started by mask, utilizing a standard anaesthesia apparatus with 35 per cent alcohol in the "ether container". Improvement was prompt, dramatic and progressive. At the end of 30 minutes she was able to sit up and speak clearly and 7 hours later she spontaneously delivered a female infant who required tracheal catheterization. Seven weeks post-partum she was free from complaints but her blood pressure was 230/120, the apex was 4 cm. outside the mid-clavicular line and there was a trace of pretibial oedema. Fluoroscopy revealed left ventricular and probably also left auricular enlargement. The final diagnosis was "hypertensive cardiovascular disease and term pregnancy".

Ethanol-oxygen vapour is apparently free of contra-indications and the authors recommend its use, independently or in combination with other measures, in acute pulmonary oedema in pregnancy.

F. J. Browne

177. **Thiouracil in Pregnancy. Its Effect on the Foetus.**

By N. ELPHINSTONE. *Lancet*, **1**, 1281–1284, June 27, 1953. 34 refs.

The author briefly outlines previous reports of the outcome of pregnancies in women treated with thiouracil. From a review of this literature it appears that only in 10 instances has any abnormality of the foetus or infant been considered to be due to the passage of thiouracil across the placenta. In most of these cases the foetal thyroid gland shows hyperplasia which slowly subsides during the first few months of life. Two babies were cretinous with swollen necks; one cretinous without a goitre; and another after 2 months became agitated and developed exophthalmos. The author then gives the case record of a baby who showed signs of hypothyroidism at birth and enlargement of the thyroid gland, and who failed to develop normally. The signs of hypothyroidism given are lethargy, infrequent crying, poor muscle tone, cool skin and persistent cyanosis of the extremities, feeble sucking, pulse-rate of 100–110 per minute and rectal temperature never above 97.2° F. during the first few days. The serum-cholesterol level was within normal limits on the 13th day. The subsequent progress of the infant was retarded and the presence of mental defectiveness is questioned.

The important point is made that the administration of thiouracil to a pregnant woman for long periods may produce thyroid enlargement in the foetus with or without hypothyroidism and possible permanent damage to the foetus. *H. H. Fouracre Barns*

178. **Prognosis in Diabetic Pregnancy.**

By W. OAKLEY. *Brit. med. J.*, **1**, 1413–1415, June 27, 1953. 6 refs.

The observations in this communication are based on two series of diabetic pregnancies: 275 dealt with at King's College Hospital (K.C.H. series) and 458 collected from other centres in Great Britain (Q series).

In the Q series 13 mothers died (2.8 per cent), death occurring from diabetic coma (8 cases, 3 of them undelivered), peritonitis (2 cases) and pneumonia, pulmonary embolism and eclampsia (1 case each). Four deaths at K.C.H. (1.4 per cent) were from pulmonary embolism, septicaemia, cholaemia and massive pulmonary collapse. All were delivered and there were no deaths from diabetic coma.

Insulin requirement rose during the 2nd and 3rd trimesters in 75 per cent of cases and the lowered renal threshold from about the 4th month made it advisable to increase the carbohydrate intake to 200 g. and to give soluble insulin in the morning as well as soluble insulin and P.Z.I. before tea. Persistent ketosis was combated by adding 20 g. of glucose to each meal. In none of the last 80 pregnancies at K.C.H. was there any significant increase in insulin requirement following pregnancy and attributable to it.

Investigation of the risk of complications during diabetic pregnancy showed no certain evidence that it caused deterioration of established retinitis. Of the last 222 diabetic pregnancies at K.C.H., 24 pregnancies in 22 women were complicated by toxaemia. One mother died of eclampsia and cholaemia and 1 had uraemia due to chronic nephritis. Follow-up of the remaining 19 cases showed residual hypertension, albuminuria or retinitis in only 6 of them and all were diabetics of old standing and, therefore, apt to develop these complications in any case.

Study of factors related to the fate of the foetus showed that:

1. Foetal loss could not be accounted for in terms of control, severity, age of onset or duration of the diabetes.
2. Toxaemia cases had only a slightly higher foetal mortality than the others.
3. In 50 pregnancies in which hormone therapy was used at K.C.H., the foetal mortality was 42 per cent.
4. In evaluating the lower foetal mortality in the K.C.H. series (21.5 per cent) over the Q series (27 per cent), emphasis is placed firstly, on close co-operation between diabetic and obstetric departments and secondly on the time and mode of delivery. At K.C.H. pregnancy is terminated at the 36th week by Caesarean section or by induction if there has been a previous normal delivery.
5. The majority of neonatal deaths occur within 48 hours and are due to respiratory failure. The neonates must be carefully nursed with adequate oxygen and temperature control and suction as necessary. No conclusive evidence was found that hypoglycaemia is related to neonatal death.

D. B. Whitehouse

179. **Cul-de-sac Aspiration and Other Diagnostic Aids for Ectopic Pregnancy. A Review of 219 Cases.**

By E. G. WINKLER and V. J. CAPRARO. *Amer. J. Obstet. Gynec.*, **65**, 340–345, Feb. 1953. 8 refs.

In 19 cases of proved ectopic pregnancy in which curettage was done decidual tissue was found in 7 only; one of the others showed a secretory and the rest a proliferative endometrium. The most important single diagnostic aid is needle aspiration of the posterior cul-de-sac which was usually done in the operating room simultaneously with examination under anaesthesia, though it may be done in the office or clinic with no more pain than ordinary venepuncture if the patient is co-operative. The cul-de-sac is entered in the mid-line using a long 15 to 18 gauge needle on a 10 to 20 ml. syringe; old blood is usually got when ectopic pregnancy is present. In 100 cases of proved ectopic pregnancy the pre-operative diagnosis was correct in 92. Cul-de-sac aspiration had not been done in any of the 8 cases wrongly diagnosed. Of the 219 cases reviewed cul-de-sac aspiration was done in 197. In 87 of these the result of aspiration was positive; in 10 of these (11 per cent) it was incorrect. In 110 the result was negative and all these were correct.

The authors classify the types of fluid aspiration with various diagnoses as follows: (*a*) clear serous straw-coloured fluid (normal, negative pelvis); (*b*) turbid serous fluid (pelvic inflammatory disease); (*c*) blood-tinged serous fluid (ruptured ovarian cyst, ovulation bleeding, occasionally pelvic inflammatory disease); (*d*) bright red grossly bloody fluid (recent bleeding

corpus luteum cyst with much bleeding, recently ruptured ectopic pregnancy with fresh bleeding, traumatic cul-de-sac aspiration); (*e*) old blood, brownish coloured fluid (ectopic pregnancy with intraperitoneal bleeding over a few days or weeks); (*f*) no return (equivocal, tap should be repeated).

In the total 197 aspirations there were 2 instances of accidental perforation of the bowel but without any bad effects. The authors feel that there are no contra-indications to cul-de-sac aspiration other than shock in the acute case where delay is unwarranted.

F. J. Browne

180. **The Diagnostic Value of Percutaneous Retrograde Arteriography of the Iliac Artery in Cases of Tubal Pregnancy.**

By U. Borell, I. Fernstrom, and A. Westman. *West. J. Surg.*, **61**, 223–228, May 1953. 5 refs. 6 figs.

The authors, working at the Karolinska Institute, Stockholm, have perfected a technique of arteriography which shows the blood vessels and placental sinuses in cases of tubal pregnancy and so is of value in the diagnosis of latent cases. They also found that straight X-rays of the abdomen are useful as these often show free fluid in the peritoneal cavity. No details of technique are given but the results illustrated are remarkable. The method is claimed to be safe and there was no ill effect in 20 cases of normal intrauterine pregnancy.

[The technique is described by the authors in *Acta Radiol., Stockh.*, **38**, 247, 1952. The femoral artery is defined at the inguinal ligament and a tourniquet applied just above the origin of the deep femoral artery. A needle is introduced (under local anaesthesia) just above the tourniquet and having perforated the artery is turned upwards and pushed 3–5 cm. into the external iliac artery. A blunt stilette is introduced to stop bleeding. Arteriography is carried out with a mixture of 1 part 22 per cent dextran and 2 parts perabrodil, the injection taking 3–4 seconds. The first film is taken towards the end of the injection and 2 others 2 and 5 seconds later. This technique outlines fibromyomata and ovarian cysts besides tubal pregnancies and would appear to warrant further study if facilities for the rapid sequence of plates are available.]

D. C. A. Bevis

LABOUR

181. **Induction of Labour: Its use and abuse.**

By A. Macfarlane. *N.Z. med. J.*, **52**, 173–184, June 1953. 18 refs.

The author condemns the use of induction of labour except for indications such as toxaemia of pregnancy, and does not favour its use himself for such conditions as minor disproportion in a multigravida.

The use of a pitocin drip for 6–8 hours on several successive days is regarded as useful for ripening the cervix in cases where induction is desirable but is not immediately urgent and the cervix is not ripe.

[This is a discursive paper and contains much of good sense. The author's attitude is that "one's approach generally to the subject of induction should be a negative one".] *L. Woodrow Cox*

182. **Uterine Inertia.**

By L. C. Hepp. *J. Amer. med. Ass.*, **152**, 894–897, July 4, 1953. 10 refs.

After a conventional account of some of the causes of inertia the author describes various methods of treatment for that form of inertia which follows active contractions.

Pitocin is the first, in doses of one or two minims intramuscularly every half hour to initiate contractions. Intravenous drip of 0.5 ml. of pitocin in 500 ml. of "glucose solution" is a useful method as it allows control of the dose by alteration of the rate of flow.

Cervical 'spasm' is best treated by dihydroergotamine (0.5 ml.) by injection or intravenously. The author has used this drug for 10 cases with dramatic results and no side effects. Though a derivation of ergot it has none of the stimulating influence on contraction of the fundus but acts by reducing sensitivity to sympathetic impulses. Delay due to contraction ring can be treated successfully by intravenous injections of magnesium sulphate, calcium gluconate or magnesium gluconate. Epinephrine or dihydroergotamine have all proved of value, but there is no mention of amyl nitrite. Willett's forceps is condemned, but it is strange indeed to read that there is still a place for the old de Ribes' bag. Caesarean section is often indicated, as when other methods have failed to excite contractions and dilate the os.

The only point in this paper is the record of the author's experience of dihydroergotamine which is contrary to that of some obstetricians. *A. Bourne*

183. **Prolonged Labour.**

By C. L. Fearl. *West J. Surg.*, **61**, 272–277, May, 1953. 1 fig. 10 refs.

The author reviews the results in a private hospital of 88 beds in which work 60 staff physicians who deliver babies. 8,785 patients were delivered in 2 years and 390 of these had a labour lasting 24 hours or more. 79 per cent of the patients were primiparae. 76 patients had a labour lasting 36 hours or more and 18 were treated successfully by intravenous pitocin infusion (5 minims to 500 ml. glucose saline given so that 0.5 minim is given per hour). The foetal loss for the whole group was 2.6 per cent, twice that for the "normal" patients.

[This is a very difficult paper to understand. In the discussion which followed it at the Annual Meeting of the Pacific Coast Obstetrical Society it is apparent that labours lasting more than 24 hours are very rare in the Western States of America and cries of horror arose when it was reported that in England patients sometimes laboured for 36–72 hours.] *D. C. A. Bevis*

184. **Effect of Forceps Delivery on the Child.**

By H. R. MacLennan, A. B. Hay, and M. L. Paterson. *Lancet*, **2**, 19–21, July 4, 1953. 5 refs.

A pilot investigation has been carried out to assess the immediate and late effects of forceps delivery on the infant. Two groups of cases were surveyed: (*a*) 167 difficult forceps deliveries (chiefly mid-pelvic) in Glasgow during 1946 and 1947 and (*b*) 148 forceps deliveries of all types in Inverness-shire during the same period. In the Glasgow group there were 11 stillbirths

(6.7 per cent) and 8 neonatal deaths (4.8 per cent), making a total foetal mortality of 11.4 per cent. Of the remaining 148 infants, personal follow-up was attempted in 121 and was successful in 90 (75 per cent). Except for one child who was mentally defective and 4 who showed strabismus, there was no evidence of abnormal defect. The total foetal mortality in the Inverness-shire group was 7.4 per cent (8 stillbirths and 3 neonatal deaths). Seventy-three infants (53 per cent) were followed up personally and no evidence of physical or mental defect observed. The findings of this preliminary survey suggest that the late results of difficult mid-pelvic forceps delivery are satisfactory although the immediate foetal mortality rate is high. The authors maintain that the operation should not be abandoned in favour of Caesarean section but that suitable cases should be more carefully selected.

H. H. Fouracre Barns

185. **Presentation and Prolapse of the Umbilical Cord.**

By R. JALKANEN and K. NIEMINEVA. *Gynaecologia, Basle*, **136**, 1–14, July 1953. 6 tables. 21 refs

The authors present two series of cases of presentation and prolapse of the umbilical cord collected at the Women's Clinic, University of Helsinki. The first series comprises 100 cases occurring between 1931 and 1939, the second 144 cases between 1946 and 1950. Cases of foetuses weighing less than 1500 grammes were omitted. The incidence of this complication over the two series was 0.42 per cent.

Aetiological factors are discussed: the most important appeared to be contracted pelvis, multiple pregnancy, prematurity, lateral insertion of the cord and malpresentation. Length of the cord, hydramnios, placenta praevia and multiparity did not appear to be significant.

Diagnosis was made on the visible presence of the cord in over half the cases. In the rest the cord was found at internal examination before or after rupture of the membranes; it was sometimes found on rectal examination. Irregularity of the foetal heart sounds was found to be the earliest sign.

Treatment consisted in the immediate adoption of the Trendelenburg position. Caesarean section was undertaken 9 times in the first series and 23 times in the second series. The trend of treatment in recent years has been in favour of more sections; replacement of the cord has become rarer and then only when delivery is quickly undertaken. Metal dilators and bags have been abandoned. Cervical incision has been practised, but has been found to yield the highest foetal mortality, especially in premature infants.

In the two series described there was no maternal mortality; foetal mortality was 32 per cent in the first series and 25 per cent in series B. Foetuses of less than 1500 grammes were not included.

In summarizing, the authors again stress the importance of the immediate adoption of the Trendelenburg position and the undertaking of Caesarean section in many cases.

[This is a sound and sensible article which puts the modern position with regard to prolapse and presentation of the cord admirably. It should be realized that this is a serious obstetric emergency and that the life of the child can only be saved by prompt action. Attempts at replacing the cord are generally fruitless and dangerous, and the choice in cases where the foetus is alive and sufficiently mature lies between Caesarean section and immediate vaginal delivery. This should be the standard teaching.]

Josephine Barnes

186. **The Problem of Prolapsed Umbilical Cords.**

By D. R. NELSON and P. H. ARNOT. *West J. Surg.*, **61**, 262–269, May 1953. 18 refs.

The authors review 22 cases occurring in 9,813 patients. Cases of presentation of the cord without rupture of the membranes are excluded. Nine cases followed artificial rupture of the membranes and 8 followed the use of Voorhee's bag although in only 4 cases was this directly responsible for the condition. Rectal and vaginal examinations in which the membranes ruptured produced 2 cases. Most of the cases occurred when the cervix was sufficiently dilated to allow rapid delivery and no Caesarean sections were performed. Six babies died but 2 were previable and 2 were dead on arrival in the hospital, giving a "corrected" mortality of 9 per cent. There were no maternal deaths.

[Parts of this paper are difficult to follow and it is impossible to define some of the causes and methods of treatment.] *D. C. A. Bevis*

187. **The Management of the First Stage of Labour in Breech Presentation.** (Die Bedeutung der Eröffnungsperiode für die Geburt in Beckenendlage.)

By S. KOLONJA and W. SCHREINER. *Gynaecologia, Basle*, **135**, 357–368, June 1953. 57 refs.

The cause of death in breech delivery is reviewed and it is shown that cerebral trauma is responsible for the great majority of foetal deaths.

In an attempt to reduce foetal mortality, a conservative approach to breech delivery was adopted in cases delivered during 1950 and 1951. Results are given of those occurring between 1940 and 1949. In the earlier period there were 685 breech deliveries: the incidence of extraction was 12.4 per cent and the corrected foetal mortality 5.9 per cent. In the second series there were 160 breech deliveries; the incidence of extraction was 3.5 per cent with a corrected foetal mortality of nil.

Peridural infiltration is under trial in breech cases and so far the results have been promising.

Josephine Barnes

188. **The Management of Breech Presentation.**

By J. MAIR. *Lancet*, **2**, 361–364, Aug. 22, 1953. 12 refs.

The author describes the method of management of cases of breech presentation adopted at the Southern General Hospital, Glasgow, since 1949. There were 71 booked breech deliveries with the death of only 1 baby —a neonatal death due to prematurity. The author maintains that there are very few cases in which there is a place for version under general anaesthesia. Hence external version is attempted under morphine gr. ¼

only. If unsuccessful, breech delivery is contemplated except in those cases where definite pelvic contraction or deformity exists. In such cases either version under general anaesthesia is attempted or elective Caesarean section carried out at term depending on the mother's age and obstetric history. From a review of the literature and from experience gained from his own series of cases, the author concludes that the foetal mortality from breech delivery increases steadily as the infant's weight rises above 6 pounds and that the ideal weight for a baby born as a breech presentation is between 6–7 pounds. In order to obtain this, routine induction of premature labour is advocated. This is done by surgical rupture of the forewaters where the frank breech is engaged in the pelvic brim. Judgment of the optimum time for induction of labour presents some difficulty and has generally been between 38th week and term. Caesarean section is advocated for the elderly primigravida with breech presentation and also for the patient with minor pelvic contraction who has been allowed to have a trial of labour and in whom the breech does not descend to the vaginal introitus.

H. H. Fouracre Barns

189. **The Hazards of External Version.**

By C. C. HALL. *West J. Surg.*, **61**, 239–254, May 1953. 86 refs.

The author reviews the literature on external cephalic version and gives his own results in 307 versions on 249 patients. In 194 cases the vertex presented at delivery (77.9 per cent success). The vast majority of the versions were done without anaesthesia or sedation. Slight bleeding followed the manoeuvre in 2 cases but both had normal deliveries at term. Two babies died but the version is not held responsible for this.

[This is a long review of current opinion on this subject and it would appear that the results depend more on the operator than on the manoeuvre itself. The author concludes with the plea that further study is undertaken to determine whether in fact version reduces the incidence of breech deliveries.]

D. C. A. Bevis

190. **External Cephalic Version.**

By M. R. FELL. *Lancet*, **2**, 364–368, Aug. 22, 1953. 14 refs.

The author has compared the results of external cephalic version under general anaesthesia with those of breech delivery over a 5-year period at the Middlesex Hospital.

The number of versions without anaesthesia was not known but it was known that no foetal or maternal death followed such a procedure. When this operation was unsuccessful version under general anaesthesia was attempted and was carried out on 102 patients (88 primigravidae and 14 multiparae) with success in 82 patients. Complications of version were 3 premature labours (1 of which resulted in a stillborn child due to prolapse of the cord), and 4 cases of accidental haemorrhage (1 of which was associated with a stillbirth). The foetal mortality from attempted version under general anaesthesia was 2 per cent and the maternal mortality nil.

There were 67 patients with breech presentations (46 primigravidae and 21 multiparae) of whom 50 had a breech delivery and 17 a Caesarean section. The maternal mortality was nil and the number of stillbirths and neonatal deaths 11, the corrected foetal mortality, i.e., in uncomplicated cases, being 6 (9 per cent).

By comparing the incidence of breech presentation at term at the Middlesex Hospital (1.35 per cent) with that where antenatal version is not practised as given by various writers (2.8–4.5 per cent) the author concludes that external version as practised at the Middlesex Hospital reduces the expected incidence of breech delivery by more than half.

From a review of the literature the author finds that spontaneous cephalic version is unlikely after the 34th week and hence states that version should be attempted after that time.

Comparison is made of the foetal mortality following on version including foetal loss in the subsequent labour, with the foetal mortality from breech presentation delivered per vaginam or by Caesarean section. In the former group 2 infants died as a direct result of version and a further 2 died in the subsequent labour (during breech delivery the version being unsuccessful) giving a total foetal mortality of 4 per cent, whereas the foetal mortality for the latter group was 9 per cent. It is therefore concluded version does result in a saving of infant life at the Middlesex Hospital. In those institutions where the foetal mortality from breech delivery is very low the value of external version under anaesthesia becomes debatable. Version is considered contra-indicated in cases where there is considerable hypertension because of the risk of accidental haemorrhage, a history of antepartum haemorrhage from the placental site, multiple pregnancy, in cases when elective Caesarean section is contemplated, and when there is a possible weak uterine scar from previous uterine operations.

H. H. Fouracre Barns

191. **Defective Blood Coagulation Associated with Premature Separation of the Placenta.**

By M. J. GOODFRIEND, I. A. SHEY, and H. L. SIEGELBAUM. *Amer. J. Obstet. Gynec.*, **65**, 1034–1037, May 1953. 14 refs.

It has been noted by various observers that blood taken from patients with severe premature separation of the placenta will frequently clot slowly or not at all. The case is reported of a negro primigravida, aged 23, who was admitted with blood-pressure 170/110, oedema and 4+ albuminuria at the 32nd week. On the 5th hospital day she developed concealed haemorrhage and after a short labour reinforced by intravenous pitocin she was delivered, by Dührssen's incisions and forceps, of a dead-born foetus. The placenta was lying partially free and was removed manually without any excessive post-partum haemorrhage. Twelve hours after delivery, however, she got suddenly worse and pressure on the fundus expressed over 1,000 ml. of semi-fluid blood. Shortly after she went into profound shock. Vaginal inspection showed that there was no bleeding from the cervical incisions but a diffuse ooze from the lower genital tract. The vagina was packed

and 2,000 ml. bank blood transfused, but she did not rally and bleeding continued through the pack. As it was felt that a defective clotting mechanism might be responsible a plasma fibrinogen level determination was done and found to be 90 mg. per cent (normal 200). She was meanwhile given 8,000 mg. fibrinogen after which the bleeding completely stopped and thereafter she made a good recovery.

The authors consider that several factors may combine to produce the bleeding diathesis. In addition to the inadequate fibrinogen level it has been shown that in abruptio placentae the concentration of Ac-globulin, which is responsible for the rapid activation of prothrombin by calcium ions and thromboplastin, falls to extremely low levels. An explanation of why bank blood may be ineffectual in replacement therapy has been given by Seegars (*Circulation*, **3**, 2, 1950) who reports that, while the prothrombin level in blood remains normal for long periods of time, Ac-globulin disappears rapidly. With fibrinogen difficult to obtain direct transfusion of non-citrated blood may be the therapeutic answer to some of the problems of blood derivative replacement. *F. J. Browne*

ANÆSTHESIA

192. **Caudal Anæsthesia in Obstetrics with Associated Relaxation Technics.**

By R. N. Rutherford, A. L. Banks, H. M. Lamborn, and J. O. Borgen. *West J. Surg.*, **61**, 285–296, June 1953. 6 figs. 12 refs.

The authors review 2,213 cases in private practice over a period of 5 years. Free choice of analgesia was excercised by both patients and physicians. The patient is put in the knee-chest position and a large pillow placed under the abdomen. A 21 gauge malleable needle 2½ inches long is then introduced into the caudal canal, the stylet removed and a 2-inch length of rubber tubing attached with a plug and adaptor on the end. Metycaine or Xylocaine is used, 10–20 ml. being injected (the concentration is not stated). Epinephrine is not used as it increases uterine bleeding and there is no advantage in using a polythene catheter instead of the needle. Anaesthesia is induced when the presenting part is on the ischial spines and the cervix well effaced and 4–5 cm. dilated. The uterine contractions sometimes cease after induction of the anaesthesia and then pitocin, 1 minim every 30 minutes, is given until efficient contractions are produced. The dose may be increased up to 3 minims but only after careful increase from 1 minim. Whatever dose produces efficient contractions is continued and it is better to use small doses frequently than larger doses at longer intervals. Rupture of the membranes is performed under prescribed conditions. Stress is laid on education of the patient and her husband in the methods of analgesia and the husbands are encouraged to stay with their wives during labour. These methods shorten the duration of labour and are completely successful in 97 per cent of cases.

[There is a great deal in this paper about induction of labour and its relationship to caudal anaesthesia and there is no doubt that the combination of methods results in rapid delivery. Those contemplating using caudal anaesthesia should certainly consult the original paper.] *D. C. A. Bevis*

PUERPERIUM

193. **Postnatal Retroversion of the Uterus.**

By D. R. Jennings. *N.Z. med. J.*, **52**, 184–189, June 1953. 4 figs.

The records of 2,593 patients at Invercargill St. Helen's Hospital were examined. In 6.3 per cent of cases retroversions were discovered post-natally on leaving hospital. Six weeks later 14.0 per cent of cases attending the clinic had retroversions. A method of replacing the uterus by attaching a volsellum to the posterior lip of cervix is described. The cervix is drawn down towards the coccyx while the operator's other hand manipulates the fundus through the abdominal wall. *L. Woodrow Cox*

194. **Mammary Abscess. Disadvantages of Antibiotics in its Management.**

By C. P. Mills. *Brit. med. J.*, **1**, 1427–1429, June 27, 1953. 2 refs.

The author describes 4 cases of acute breast infection to illustrate how the clinical features of acute pyogenic infections may be altered by antibiotic treatment and the timing of surgical interference may consequently be difficult to judge.

In the first 2 cases the symptoms and signs of acute breast abscess were so altered by prolonged penicillin therapy that the condition was difficult to judge from lactation carcinoma. An indurated, non-fluctuant and fixed mass was present in each case with very little evidence of acute inflammation. Surgical drainage revealed a dense hard mass of fibrous and granulation tissue surrounding a loculus of pus, the procedure being accompanied by considerable haemorrhage. In the remaining 2 cases the clinical picture of acute breast abscess was similarly modified to such an extent by antibiotics that the delay in operative drainage led to a long and tedious recovery. The organism responsible in each case was *Staphylococcus pyogenes* and treatment was primarily with penicillin, one case receiving in addition a 7-day course of chloramphenicol.

The author comments on the limitations of antibiotics in a casualty department. Used early, they may completely abort severe infections but, when administration has been delayed until infection is firmly established, resolution unaided is unlikely. Timely surgical drainage is no less necessary in this type of case than previously, though this is often not apparent at the time. *D. B. Whitehouse*

THE INFANT

195. **An Investigation into the Prognosis of Premature Births during the Years 1915–1925.** (Untersuchungen über das Schicksal der Frühgeburten der Jahre 1915–1925.)

By R. Knoepfli. *Gynaecologia, Basle*, **135**, 368–390, June 1953. 10 figs. 10 refs.

Premature births were divided into 8 groups on the basis of birth weight between 900 and 2,500 grammes. A series of 1,149 infants were studied. The incidence of premature birth was found to be 7.8 per cent. Twins are an important factor.

Mortality is closely related to birth weight. Over 50 per cent of those under 1,900 grammes do not survive, while mortality in the group 2,300 to 2,500 grammes is only 13 per cent. Mortality is higher in male infants. Mortality is higher in multiparae than in primigravidae and higher in illegitimate than in legitimate children. Mortality is lowest with spontaneous delivery and higher with operative delivery, including Caesarean section.

A slight but definite fall in mortality of premature infants was noted in the years 1939 to 1948 compared with 1915 to 1925, but this was only found in infants over 1,700 grammes.

The most important cause of death is immaturity for extra-uterine life. *Josephine Barnes*

196. **Plural Births in the United States.**

By J. B. NICHOLS. *West J. Surg.*, **61**, 229–236, May 1953. 6 tables.

The Advisory Medical Director of an insurance company has reviewed the statistics for multiple births in the U.S.A. for the period 1915–1948. The figures include only those cases where at least 1 child was born alive; births where all the children are stillborn are excluded. 1,578,670 births are considered from a total of 73 million. Twin births average 23,600 a year, triplets 235 and quadruplets 3 or 4. The greatest number of plural births occur at higher age groups (35–39 years) and are more frequent in coloured races. The number of accouchements for each case are: twins 90, triplets 9,126, quads 634,064. The average is 89. The stillbirth rate is considerably higher than average in plural births as is also the mortality during the first 6 months of life. The sex distribution varies in different categories, relatively more males being born in twin pregnancies and more females in quads and quins. There appears to be a definite genetic or biological propensity to repetition of plural births.

[This can fairly be called a large series of cases. The paper should be read in its entirety.]

D. C. A. Bevis

197. **Anomalies of the Stomach and Small Intestine.**

By P. CRABTREE. *West J. Surg.*, **61**, 301–314, June 1953. 32 refs.

The author gives his results in 13 cases of intestinal obstruction operated upon in the first few days of life, one being a premature infant of 2 pounds 2 ounces. Early diagnosis and treatment are essential as the expectation of life without surgery is about 6 days. When vomiting occurs in the first day or two of life its cause must be found without delay. With complete obstruction of the upper intestinal tract vomiting begins within 8–10 hours and soon becomes projectile. Incomplete obstruction may not give trouble until food, etc., blocks the opening and the obstruction becomes complete; enterogenous cysts often do this. Blood may appear in the vomit and the presence of bile depends on the site of the obstruction. The character of the stool is important. The typical meconium stool soon after birth should not be delayed and milk curds should be present after 24 hours. The presence of cornified squamous epithelial cells is also sometimes of help. Sometimes the baby with even a complete obstruction may have several mucous stools and these may be green in colour. The findings on examination of the infant depend on the time at which it is seen. Most are perfectly normal at birth and remain so until the gut begins to fill with swallowed air and food. Dehydration is usually less marked than would be expected. Rectal examination must always be done. Laboratory tests are usually of little value. X-rays are helpful but it must be remembered that relatively large amounts of gas in the bowel are normal and diagnosis rests on observing abnormally large amounts of gas and in these cases the pressure of the distended loops on each other causes a " squaring off " of the shadows. If there is any doubt about interpretation it is as well to repeat the X-ray in a few hours time and observe if there is any increase in the distension. Radio-opaque substances should not be used as they are not without danger and the air in the gut is a good contrast medium. The pathology is varied and treatment depends, of course, on what is found. No child should have surgical intervention withheld whatever its condition but gastric lavage, warmth, correction of electrolyte imbalance and blood transfusion materially increase the chance of success. The choice of anaesthetic is secondary to choice of anaesthetist. The procedure performed should be the simplest for correcting the abnormality and establishing gastrointestinal continuity; great care must be taken to ensure that continuity has in fact been established as bands and septa are frequently multiple. In general, side to side anastomosis is recommended. Iliostomy should never be performed as it is impossible to maintain electrolyte balance. Postoperative care is important and gastric suction is maintained for 72 hours. Feeding is not started until peristaltic sounds are heard and then glucose water is given. If vomiting occurs, feeding is discontinued and suction restarted for another few days until the oedema round the anastomosis has subsided. All children are nursed in incubators and given oxygen as needed. Antibiotics are given to prevent pulmonary infections rather than to control peritoneal infection. Blood transfusion is also used as required. Following these methods only 3 babies died from the immediate operative procedure.

[This is an extremely good review of a difficult subject.] *D. C. A. Bevis*

198. **Hæmolytic Disease of the Newborn: 1.—Laboratory Aspects.**

By F. W. GUNZ. *N.Z. med. J.*, **52**, 156–159, June 1953.

The author recapitulates the diagnosis and divides cases into 3 groups: mild cases with good prognosis, i.e. those with 3 million red cells and 60 per cent haemoglobin or better at birth; moderate cases with doubtful prognosis, those with 2–3 million red cells and moderate jaundice at birth; and severe cases with

poor prognosis, those with deep jaundice at birth irrespective of blood count.

199. **Hæmolytic Disease of the Newborn: 2.—Diagnosis and Management.**

By M. McGeorge. *N.Z. med. J.*, **52**, 159–164, June 1953.

For treatment the author has had good results using repeated small transfusions of about 100–120 ml. of blood, rather than by replacement transfusion. There were 4 deaths in 34 cases of simple repeated transfusion, 5 in 7 cases of replacement transfusion and 3 in 4 cases not transfused. Only 3 of the 12 fatal cases could be regarded as falling in the moderately severe group.

200. **Hæmolytic Disease of the Newborn: 3.—Obstetric Aspects.**

By B. W. Grieve. *N.Z. med. J.*, **52**, 164–167, June 1953. 2 refs.

The author discusses the pros and cons of premature induction of labour, and gives results for 1952 from the Cornwall Hospital Auckland.

Induction of labour: 22 cases, foetal mortality 7 (31.7 per cent).

Spontaneous labour: 14 cases, foetal mortality 2 (14.3 per cent).

These figures are similar to those of Mollison (*Lancet*, **1**, 429, 1952) and in Auckland the practice of induction of labour is now less frequently performed.

L. Woodrow Cox

201. **Transient Hypothyroidism in a Newborn Infant.**

By D. Morris. *Lancet*, **1**, 1284–1285, June 27, 1953. 5 refs.

The author reports the outcome of a pregnancy in which the mother was treated with methyl thiouracil throughout the pregnancy for thyrotoxicosis. A baby weighing 5 pounds 4 ounces was delivered at term. The baby was very inactive, reluctant to suck, had a cold dry skin, a pulse rate of 120 per minute and a palpable thyroid gland. Serum-cholesterol was 312 mg. per 100 ml. Treatment in the form of thyroid by mouth was given for 10 days with dramatic improvement. Subsequently the baby's progress was retarded and there was a mild degree of hydrocephaly which was considered to be coincidental. The point is made that since thiouracil is excreted in the milk the baby should not be breast-fed. *H. H. Fouracre Barns*

202. **Raised Incidence of Infections in Infants Born to Mothers with Infection of the Urinary Tract at the Time of Delivery.**

By H. Zilliacus and L. E. Tötterman. *Gynaecologia, Basle*, **135**, 353–357, June 1953. 5 refs.

In records of 9,607 deliveries, 279 cases were found in which the mother had given birth to a full-time normal child by cephalic presentation but had at some time during her stay in hospital suffered from infected urine. These were compared with 558 controls, that is, the normal case immediately preceding and immediately following one with urinary infection.

The total neonatal morbidity was found to be 20.1 per cent in the infants whose mothers had urinary infections, as against 8.1 per cent in the controls. The highest percentage was infections of the skin, navel and eyes; the infants whose mothers had urinary infections showed 10.8 per cent of such infections as compared with 4.7 per cent in the controls. Two infants died of infection, 1 in each group. It is suggested that virulent infection of the vulva exists in mothers with urinary infection. *Josephine Barnes*

203. **Incidence of Neonatal Infection in Hospital and Domiciliary Midwifery.**

By V. M. Crosse and J. M. Mackintosh. *Brit. med. J.*, **1**, 1374–1375, June 20, 1953. 3 tables.

The infection risk for infants born in hospital and at home was compared by analysis of records for 12 months of 1,459 infants born at Sorrento Hospital, and 1,846 delivered by 22 domiciliary midwives in Birmingham. Stillbirths, transfers and deaths within 48 hours were excluded, leaving 1,336 hospital and 1,788 domiciliary cases for comparison.

The following definitions of infection were used: discharge from the eye lasting at least 24 hours, sore buttocks, skin spots, umbilical infection and otitis media. On this basis, the infection rate was 10.48 per 100 hospital babies and 14.48 for domiciliary babies. The commonest infection in each group was slight ophthalmia (7.12 per 100 babies in hospital and 10.97 at home). The risk of skin infection was greater in hospital where the rate was 2.54 per cent as opposed to 0.84 per cent at home, which confirms the potential dangers of cross-infection in an institution. However, the baby born at home is liable to contract infection from unmasked relatives and visitors with respiratory infection, and in this investigation 1.56 per 100 of infants born at home had nasal or ear discharge or pulmonary infection, while no such complications were recorded in the hospital group. *Doreen Daley*

204. **Cyanosis in Newborn Babies caused by Aniline-Dye Poisoning.**

By J. D. Pickup and J. Eeles. *Lancet* **2**, 118, July 18, 1953. 3 refs.

The authors report 5 cases of methaemoglobinaemia in newborn infants due to absorption of aniline compounds from marking ink used to mark napkins. The aniline-dye poisoning results from cutaneous absorption or inhalation. Attention is drawn to the danger of bronchopneumonia as a signal to the poisoning, especially when the child is in an incubator or oxygen tent, where a high concentration of vapour from the aniline may be built up. The importance of boiling before use all clothing or bedding marked with aniline ink is stressed. *H. H. Fouracre Barns*

MATERNAL MORBIDITY AND MORTALITY

205. **Post-Partum Venous Thrombosis and Leg Ulcers.**

By S. T. Anning. *Brit. med. J.*, **2**, 14–16, July 4, 1953. 8 figs. 6 refs.

The author, from the General Infirmary at Leeds,

examined 557 women with leg ulcers of whom 160 had suffered from post-partum venous thrombosis. The majority were between 35 and 60 years of age, and were seen at varying periods after their confinements. He found that venous thrombosis occurred after the first confinement in 50 per cent of his patients, after the second in 22.7 per cent and after the third in 25 per cent. The increase fell even more after the fourth, fifth and sixth confinements.

Information was obtained about the confinements followed by thrombosis. In 31.2 per cent there was some intervention, such as forceps delivery. The incidence of long labour and post-partum haemorrhage was also high. A family history of varicose veins, thrombosis and leg ulcers was found in 52 per cent of those whose history was known. Thirty-eight per cent of the patients at the time of examination were regarded as overweight. The author feels that special precautions should be taken to prevent venous thrombosis in primigravidae with a positive family history, and who have difficult labours. *Eileen Wilson*

206. **Acute Adrenal Cortical Failure as a Cause of Shock and Death.**

By E. S. TAYLOR and L. L. ESSIG. *Amer. J. Obstet. Gynec.*, **65**, 720–732, Apr. 1953. 5 figs. 14 refs.

The authors believe that adrenal cortical failure may be a cause of fatal shock after operations and sepsis, including septic abortion. They review 6 of their cases, 3 of whom survived and in the others postmortem examination showed atrophy and cell degeneration of the adrenal cortex with reduced cell content of lipids. They regard the following as important in diagnosis: delayed shock unrelated to depleted blood volume and unresponsive to blood replacement; marked hypotension; rapid pulse; cyanosis of fingers, toes, neck and face; profuse diaphoresis; pain and tenderness over the kidneys; extreme thirst; hyperpyrexia; mental confusion followed by coma; oliguria; cold and clammy skin; raised level of non-protein nitrogen in the blood; raised serum potassium and decreased serum sodium and chlorides; albuminuria.

In treatment, if there is severe dehydration, parenteral fluids including glucose and sodium chloride, plasma or blood should be given and vasopressors to raise blood pressure. Desoxycorticosterone acetate (DCA) in oil 10 mg. intramuscularly should be given at once and repeated in 12 hours and then 10 mg. daily. Cortisone 100 mg. intramuscularly is given immediately and then 50 mg. every 6 hours. Aqueous adrenal cortical extract 30 ml. intravenously in 1000 ml. of 10 per cent glucose in saline should be given immediately and repeated as necessary. ACTH is useless.
F. J. Browne

GYNÆCOLOGY

207. **Pelvic Venography Through the Clitoris.** (Phlebographie pelvienne chez la femme par le clitoris (Pelvivenographie).)

By S. PETKOVIC. *Gynaecologia, Basle*, **136**, 43–51, July 1953. 11 figs. 14 refs.

A method of radiological visualization of the pelvic veins by injection of a radio-opaque medium into the clitoris is described. This has been performed in 35 cases. Puncture is made just above the clitoris, using a needle large enough to permit rapid injection. Blood should flow into the needle at a depth of 2 mm. If blood does not appear instantly, a little saline is injected and if this enters quickly and without pain, the vein has been entered. Fifteen to 20 ml. of the radio-opaque medium is injected and the picture taken at the end of the injection. The solution has been shown to disappear 3 minutes after the injection. The solution employed has been "Juduron" (Cilag) 70 per cent. No serious effects have been seen, though slight constitutional disturbance is noted in some cases. Extra-venous injection is without serious consequence. By this means the veins of the clitoris and bladder are shown and the internal branches of the hypogastric veins, leading to the common iliac. The inferior vena cava is rarely seen.

The method is useful in the diagnosis of pelvic venous thrombosis. In cases of cancer of the cervix changes are seen in the pelvic veins. After radiotherapy, the veins are narrowed. Venous compression may be demonstrated in cases of pelvic tumour. In pregnancy the veins are dilated and varicosities may be seen. *Josephine Barnes*

208. **Peptic Ulcer in Women.**

By D. H. CLARK. *Brit. med. J.*, **1**, 1254–1257, June 6, 1953. 8 figs. 11 refs.

Following several suggestions that have been made regarding the influence of menstruation and pregnancy on peptic ulceration, the natural history of the disease has been investigated by interviewing 400 women with proved ulcer. They were aged 21–74 years and in most cases had had more than 5 years' symptoms. The ulcer was duodenal in 330 cases and gastric in 70. Care was taken by the questioner to eliminate suggestion.

Of the 291 patients who had had ulcer symptoms before the menopause, 28 per cent claimed cyclical exacerbation, usually for a few days premenstrually but occasionally it had persisted through the period. On the whole, it was concluded that the effect of menstruation on ulcer symptoms is inconsiderable and any apparent relationship may be functional.

One hundred and eighteen of the patients had had 344 pregnancies and of these 313 had occurred subsequent to the onset of the ulcer. Assessment of change in ulcer symptoms was complicated by the gastric disturbances commonly present in normal pregnancy but this was taken into account in drawing conclusions which were based on the patients' views regarding the origin of the symptoms and their severity. It appeared that pregnancy was associated with a remission of the ulcer in 88.2 per cent from an early stage until term and more than half of these had been completely symptom-free. The remaining cases were not improved, a few of them being worse in pregnancy. Three months post-partum the beneficial effect of pregnancy seemed to be at an end and every patient suffered recurrence of symptoms within 2 years. Several of them noticed dramatic improvement during successive pregnancies.

The menopause had been reached in 204 of the women and their histories showed the peaks of incidence of the onset of symptoms in late adolescence or early adult life and also at the menopause. At the latter period there was a high incidence of increased symptoms and of complications in those women previously suffering from ulcer.

In discussion, the author speculates that the remissions of ulcer symptoms in pregnancy and the frequency with which they start, flare-up or cause complications at the menopause, may be of psychical or hormonal origin. There is no proof of the latter and so far hormone therapy has been disappointing.

Doreen Daley

209. **The Effects of Estrogens and Other Steroids on the Pituitary Gonadotrophins in Women.**

By W. E. Brown, J. T. Bradbury, and E. C. Junck. *Amer. J. Obstet. Gynec.*, **65**, 733–747, Apr. 1953. 12 figs. 13 refs.

By giving oestrogen in varying doses to rats, weighing the pituitaries and ovaries 48 to 120 hours later, and assaying the pituitary potency (content), it was found that approximately 72 hours after injection of oestrogen and continuing till about 96 hours after the injection there is a rise in weight of the ovary suggesting a release of gonadotrophin from the pituitary. The potency (content) of the pituitary remained the same for 72 hours but after that was reduced, suggesting that the gonadotrophin had been released. These experiments suggest that there is an initial stimulation of pituitary activity by oestrogens which reaches its peak at about 96 hours and is followed by release of gonadotrophin as manifested by an emptying of the gland and stimulation of the ovaries.

To women gradually increasing doses of oestrogen were given daily from the 1st to the 30th post-menstrual days. This produced anovulatory cycles suggesting failure of gonadotrophic stimulation of the ovary. In the same group of women at a later date oestrogen administration was begun on day 15 of the cycle and continued till the onset of bleeding or until day 28. These women bled from a normal secretory endometrium and at the proper time. It would therefore seem that oestrogen at this time had no effect on the luteotrophic activity of the pituitary or on the existing corpus luteum.

To another group of women with regular ovulatory cycles a single dose of 20 mg. of stilboestrol was given orally between days 5 and 8. Weekly endometrial biopsies showed that there was a delay in the onset of the next period, and that this was due to delay in ovulation. Urinary studies showed that there was a considerable increase of gonadotrophin which was recovered in the urine 48 to 96 hours after the oestrogen was given. These experiments suggest that the gonadotrophin was released from the pituitary between the 5th and 8th days, at a time when a release does not normally occur and when the follicle was too immature to respond by ovulation. Normal ovulation, however, occurred 15 to 20 days later. It seems therefore that a single dose of oestrogen early in the cycle temporarily delays ovulation and is followed by a normal ovulatory pattern in the current and subsequent cycles. This delay in ovulation is associated with a premature release of gonadotrophic hormone in the urine. If the oestrogen is administered after ovulation there is no change in the endometrial pattern. The continuous administration of oestrogen begun in the pre-ovulatory interval prevents ovulation during that cycle probably by inhibiting the recovery of the pituitary during its administration.

The authors conclude that the initial response of the pituitary to oestrogen is the release of gonadotrophin and that the so-called suppression effect is really a depletion or exhaustion effect and the continued administration of oestrogen prevents recovery of the pituitary—hitherto called a depression.

F. J. Browne

210. **Hyperestrinism in Old Women: Report of a Case with Cortical and Medullary Hyperplasia of the Ovaries and Possible Adrenal Hyperactivity.**

By R. E. Scully. *Amer. J. Obstet. Gynec.*, **65**, 1248–1256, June 1953. 7 figs. 15 refs.

Postmenopausal hyperoestrinism is usually due to an ovarian tumour or a decreased inactivation of oestrogens by the liver in liver disease or vitamin B complex deficiency. The author describes a case of a 73-year-old woman who had postmenopausal haemorrhage associated with carcinoma of the corpus uteri. There was evidence of hyperoestrinism in that the vagina contained 76 per cent of cornified cells though the endometrium, uninvolved by tumour, was not hyperplastic. Panhysterectomy was done and the removed ovaries showed in the cortex nests of eosinophile cells resembling luteinized theca cells and also ill-defined zones of lutein cells. In the medulla there were nodules of hilus cells. A remarkable feature was that the marked oestrogen effect persisted in the vaginal smear for 2 years after removal of the ovaries suggesting that the adrenal cortex must also have been, and remained, hyperactive. Novak in 1950 reported endometrial hyperplasia 14 years after bilateral oöphorectomy. The author concludes that the postmenopausal hyperoestrinism may have been due to the new cells in the ovarian cortex as well as the hilus cells, with possible adrenal hyperactivity.

F. J. Browne

211. **The Detection of Chromosomal Sex in Hermaphrodites from a Skin Biopsy.**

By K. L. Moore, M. A. Graham, and M. L. Barr. *Surg., Gynec. Obstet.*, **96**, 641–648, June 1953. 2 figs. 19 refs.

The authors briefly summarize the work which has been done in animals, revealing the presence of distinctive nuclear morphology according to sex. This has been demonstrated most clearly in the nerve cell nuclei of cats. In the female, in addition to the large nucleolus the nucleus contains a chromatin mass about 1 micron in diameter. A chromatin body of similar size is seldom seen in nerve cell nuclei of male cats.

The chromatin mass is called the sex chromatin in view of its size in relation to sex and there are good reasons for inferring that it is derived from the sex chromosomes, although direct proof is lacking.

With this as a background, a systematic study of nuclei in human skin was made. Skin was used because of the availability of this tissue as a biopsy in clinical medicine.

Specimens of skin from 50 normal female and 50 normal male subjects were studied. The specimens were fixed for 24 hours in a modified Davidson's solution (the glycerine was omitted) and were then immersed for 24–48 hours in 70 per cent alcohol. Routine embedding in paraffin was followed by sectioning at 5 microns. Sections stained with haematoxylin and eosin proved quite satisfactory for the identification of sex chromatin. The sections were studied with an oil immersion objective, attention being directed toward the nuclei of the Malpighian layer of the epidermis. A minimum of 100 nuclei selected at random were examined and the incidence of visible sex chromatin recorded as a percentage figure.

In the 50 female specimens examined the sex chromatin was visible on an average in 69 per cent of the nuclei. In most nuclei it consisted of a plano-convex body lying against the nuclear membrane.

In the 50 male specimens on an average only 5 per cent showed a small chromatin mass which may or may not have been sex chromatin.

The evidence available to date indicates that the X chromosomes and the small Y chromosomes of male nuclei fail to form a chromatin mass of sufficient size to be distinguished from the general particulate chromatin in most cells.

The authors have studied skin biopsies from 2 cases of hermaphroditism. The first was a case of female pseudohermaphroditism with the adreno-genital syndrome. A skin biopsy was studied at the age of 14 months and sex chromatin was visible in 75 per cent of the nuclei. At laparotomy the uterus, tubes and ovaries were normal and a biopsy from one gonad showed typical ovarian structure.

The second was a case of male pseudohermaphroditism. In a skin biopsy a chromatin mass was seen in only 4 per cent of nuclei. Biopsy from both gonads consisted of testis tissue.

It is concluded that the chromosomal sex is as clear in somatic nuclei of hermaphrodites as it is in normal individuals. The authors believe that in cases of doubt, the skin biopsy technique may prove to be a simple method of detecting the dominant sex in infancy. They end with a plea for the application of the technique in other cases of intersexuality in the hope of clarifying the complex problem of hermaphroditism.

John P. Erskine

212. **Study of Hydrosalpinx by Means of Kymographic Insufflation.** (Étude des hydrosalpinx par l'insufflation kymographique.)

By L. Bonnet. *Gynéc. Obstét.*, **52**, 56–74, 1953. 11 figs.

The variety of hydrosalpinx referred to is that which was described by Claude Béclère under the name of Cystic Valvular Salpingitis: the soft texture of this type of inflammatory reaction is what is characteristic. This is why they remain clinically latent and up to the present time salpingography has been the only method of revealing their existence and their frequency.

The writer suggests the use of the term "pseudocystic tubal dilatation" as being preferable in view of the fact that an inflammatory origin has been questioned in a number of cases.

Following detailed experiments with his own kymograph the writer concludes that the capacity of the tubal cavity can be determined by comparing the obliquity of the initial tracing and of the final tracing with those of his model tracings made according to a standard using a cavity of 30 c.cm. and increasing this by 10 c.cm. with each subsequent insufflation. By means of a mathematical formula the capacity of any dilated tube can be measured.. Additional diagnostic aids include pain referred to the side concerned, sometimes associated with a "blowing-up" sensation. In addition an adnexal mass can be felt immediately after the act of insufflation, and this is very tender: the vital point is that it did not exist before the insufflation. This mass can be as big as a tangerine orange.

D. Maxwell

FUNCTIONAL DISORDERS

213. **Uterine Bleeding, Functional, Ulcerative and Congestive.**

By M. C. Watson, J. Harkins, and W. Paul. *Canad. med. Ass. J.*, **68**, 548–552, June 1953

The authors describe this paper as a preliminary report detailing a new and more simple classification of uterine bleeding. This they hope will clear up the present confused classification. Pregnancy haemorrhages are not considered, neither is bleeding due to functioning ovarian tumours, or post-menopausal bleeding. Subsequent papers will examine the aetiology, pathology, histology and treatment in detail.

The classification is as follows:

Uterine Bleeding

1. *Functional bleeding*
   - *a. Withdrawal bleeding in health*
     1. Menstruation.
     2. Excessive bleeding at the menarche.
     3. Irregular bleeding at the menopause.
   - *b. Withdrawal bleeding in disease*
     1. Prolonged oestrin effect.
     2. Prolonged progestin effect.
     3. A fixed pattern of ovarian function.
2. *Ulcerative bleeding*
   - *a.* Simple bleeding.
   - *b.* Malignant.
3. *Congestive bleeding*
   - *a.* Varicosities.
   - *b.* Mechanical.
     1. Adhesions (post inflammatory).
     2. Tumours.
     3. Misplacement.

Each section of the classification is then considered and the following conclusions emerge.

Excessive bleeding at the menarche is one of the prodromal symptoms of menstruation resulting from lack of development of the regulating mechanism. As soon as this is established regular menstruation occurs.

Irregular bleeding at the menopause is due to an ageing process in the ovary, usually with failure of luteinization. The uterus also undergoes ageing, and the accompanying vascular changes aggravate the bleeding. (This statement we hope is made after malignancy has been excluded.)

Withdrawal bleeding in disease is due to a prolonged oestrogen effect, as a result of the failure of the follicles to rupture, and the consequent prolongation of the proliferative type of endometrium. There is no permanent damage to the ovary, the bleeding is venous and rarely enough to demand transfusion—treatment is by restoration to normal health.

Prolonged progestin effect produces a prolonged secretory effect on the endometrium, accompanied by lutein cysts of the ovary. This is due to an imbalance between the pituitary gonadotrophin production and ovarian hormone production at the extremes of menstrual life.

In these cases there is detectable enlargement and softening of the uterus. The bleeding is sudden, depleting and frequently mistaken for an early abortion. Urgent treatment is necessary, with a conservative approach to the younger patients and a radical approach to the older.

A fixed pattern of ovarian function—this may result from hereditary developmental defect or acquired permanent damage from infection, metabolic disease or avitaminosis.

The ovary may atrophy or become cystic from abortive attempts at follicular formation. The result is either an atrophic or hyperplastic endometrium with ovulation rarely occurring. The symptoms and signs have their basis in ovarian deficiency which is progressive and no treatment will have any effect, least of all removal of ovarian tissue.

The condition may start in childhood and apparently includes abnormal sexual and marital problems of every conceivable kind, irregular or prolonged uterine bleeding, pelvic pain, sterility and menopausal upsets of emotional and vasomotor type.

Coincident with damage to the ovary, careful history and physical examination will usually elicit evidence of faulty nutrition in other parts of the body.

Ulcerative bleeding

The benign type exactly resembles oestrin withdrawal bleeding—and so rather confuses the classification.

Malignant ulceration is briefly considered.

Congestive Uterine bleeding

This is due to back pressure from varicose veins of the broad ligaments and endometrium—these are said to be located just above the internal os.

The mechanical type is ascribed to adhesions associated with post-inflammatory conditions which also produce venous congestion.

[The concept of functional uterine bleeding as a series of different types of withdrawal bleeding seems valuable. The syndrome of fixed ovarian function is abstracted in detail as there are many who may not agree with the authors' ideas. Also surely the upset of ovarian function resulting from inflammatory disease is due to the inflammatory change in the ovary, rather than to the mechanical effect of the adhesions.

In summary, this paper produces a good classification, which is occasionally obscured by over-explanation.] *R. A. H. Kinch*

214. **Secondary Amenorrhœa.**

By S. M. MARTINS. *West J. Surg.*, **61**, 332–338, June 1953. 1 fig. 10 refs.

Thirty-six patients attending the Los Angeles Maternity Service were found not to be pregnant and their amenorrhoea was investigated. Diet and dietetic habits seemed to play an important role, almost all the patients being on a high carbohydrate diet and little meat, milk or eggs was eaten. The majority also ate little fruit, vegetables or whole grain cereals. Overweight was particularly noticeable, almost 25 per cent weighing 200 pounds and over. Two-thirds of the patients gave a history of sudden weight gain at the beginning of their amenorrhoea and these patients were 20–30 pounds heavier than patients in an apparently normal group. The psychic and emotional states of the patients were unstable and 20 of the patients had symptoms of pregnancy (nausea, etc.). No definite endocrinological defects were discovered and only 1 patient was anaemic. The blood sugar was within normal limits in 28 patients tested and the blood iodine concentration normal in 27 out of 30 patients tested. Seven out of 19 patients had secretory endometrium on biopsy. The incidence of treated and untreated syphilis was 54 per cent compared with 14 per cent in the maternity clinics generally.

D. C. A. Bevis

215. **Initiation of Ovulation by Infiltration of the Superior Sympathetic Cervical Ganglion.** (Declanchment de l'ovulation par l'infiltration du ganglion sympathique cervical superior.)

By A. NETTER and A. LAMBERT. *Riv. Ostet. Ginec.*, **8**, 77–82, Feb. 1953. 6 refs.

The authors drew attention in 1944 to the results which they had obtained in the treatment of amenorrhoea and in sterility associated with lack of ovulation, by infiltration of the superior cervical sympathetic ganglion with Novocaine. The rationale is based on the belief that such infiltration modifies the action of the pituitary gland. The senior author has published (*Presse méd.*, 1944, **52**, 117) results of 2 years experience with this method which proved encouraging, having obtained 14 cures in 20 cases of amenorrhoea. They published, also, the effect of such infiltration on anovulatory menstruation and on cases of metrorrhagia of metropathic type. The authors now record their methods and experience of the past 10 years which confirm their previous results.

Since their first publication other authors have confirmed their work. For example, Canon and Paquet of Brussels reported in 1948 18 cases of amenorrhoea treated by such infiltration. Pirard of Verviers reported successful treatment by this method and had observed 5 cases of pregnancy following infiltrations of the superior cervical ganglion. Liesse had infiltrated the

stellate ganglion and reported 2 cases of successful ovulation.

The technique used was described by Orsoni in 1948. 10 ml. of a 1 per cent solution of Procaine is injected with a 6 cm. needle. The patient sits and looks straight in front of her. The needle is inserted at the point of intersection of a line passing vertically from the tip of the mastoid process and a line passing horizontally 1 cm. beneath the angle of the mandible. The needle is passed perpendicularly into the skin for a distance of 2–5 cm. when the point will reach bony resistance. This is the vertebral body. The needle is withdrawn 2–3 mm. The direction is slightly changed to point forwards and is passed for 2–3 mm. along the anterior surface of the vertebral body. The test of successful injection is the appearance of the Horner syndrome of myosis, enophthalmus, sweating and congestion of the half-face. Difficulty may be encountered if the needle passes into the tough intra-transverse ligaments. Should this happen, the needle should be withdrawn and passed a little further forward. On the other hand, if one is too far forward the vertebral body would be missed. The injection appears easier upon the right side than on the left for a reason not understood by the authors. They never observed a serious accident due to the injection. Aspiration with the syringe is necessary before the injection because of the possibility of withdrawing cerebro-spinal fluid or blood. Following bilateral infiltration there may be a temporary paralysis of the larynx.

The authors begin by infiltrating the right cervical ganglion with 10 ml. of Procaine. If this is followed by no disagreeable reaction, one week later they perform a bilateral infiltration. The full treatment comprises 6 bilateral infiltrations at weekly intervals. The authors studied 92 cases of amenorrhoea of at least 6 months' duration. They chose the types of amenorrhoea believed to be of pituitary rather than of ovarian type. Estimations of F.S.H. in the true pituitary types show a lowered urinary output as opposed to the ovarian type of amenorrhoea which is associated with a raised F.S.H. An organic type of amenorrhoea was excluded, such as that due to tumours, cachexia, or tuberculosis. All cases were examined completely and the lungs and sella turcica were X-rayed. Of 97 cases of secondary amenorrhoea 45 had re-established regular periods and 12 irregular periods by this method of treatment. Of 15 cases of primary amenorrhoea, 10 were cured. The authors also treated 18 cases of anovulatory cycles based on temperature studies and endometrial biopsies, pregnancy following in 8 cases. The authors also claim successful treatment of metropathia haemorrhagica by these infiltrations.

In discussing their results, the authors emphasize that a large number of cases of amenorrhoea end in spontaneous cure. Even by eliminating cases of amenorrhoea of less than 4 months' duration, the authors consider that a number of spontaneous cures must still occur amongst their so-called successful cases. They advance the hypothesis that the pituitary gland is innervated by the sympathetic cervical ganglion and therefore it is possible to modify the gonadotrophic hormone secretion, but realize that further studies are necessary to prove this. They consider that this is a relatively simple and harmless method of treating amenorrhoea and disturbances of ovulation. *Patrick Steptoe*

216. **Studies on the Comparative Statistics of the Menopause.** (Recherches sur la ménopause—études de statistique comparative.)

By M. TISSERAND-PERRIER, *Gynéc. Obstét.*, **52**, 43–55, 1953. 3 figs.

The statistical material concerned consists of 814 physiological menopauses in 700 married and 114 single women and 151 artificial menopauses in 141 married and 10 single women. The average age of the physiological menopause was 48 years 5 months and 3 days, and a comparable figure given by the Social Security Authorities was exactly the same.

The place of origin of the woman seems to have some effect on the exact age of the menarche. The average age in Paris is $\frac{1}{2}$ to 2 months earlier than the general average; it is 3 months later in Brittany and 5 months later in the Centre or South West of France. As regards the menopause, the average age is earlier in the Brittany women and later in those coming from the Centre or South West. Occupation plays a part. The more this exposes a woman to fatigue the earlier is her menopause. It was noted that women living in the country had, on the average, a later menopause than those living all their life in a town.

When menstrual life is short the number of children is the same as when it is long.

There seems to be a relationship between longevity and the menopause amongst women older than 70, as in them the menopause is on an average later. Unmarried women have less in the way of hot flushes than married ones. They also have less functional disturbance, less obesity, and less floodings. The figures suggest that women with a history of floodings have a later menopause.

Women who have had several miscarriages have a more precocious menopause. There is no correlation between the date of the appearance of the periods and the date of the menopause. A clinical study shows that the final arrest of the menses is frequently associated with a confinement, illness, operation or nervous shock. *D. Maxwell*

217. **Female Fertility.**

By D. LLEWELLYN-JONES. *Brit. med. J.*, **2**, 180–182, July 15, 1953. 1 fig. 14 refs.

The author undertook a survey at Salford, Lancashire, to determine the average interval between the desire to conceive and the conception. All the patients —1,202 women—were primigravidae attending the Hope Hospital. If conception occurred within 9 months, no further questions were asked. If later, coital habits, contraceptive technique, and the absence of the husband from home were considered. Where contraception was used, the calculation was made from the date of the abandonment.

It was found that 90.25 per cent were pregnant within one year of desiring to conceive, and 94 per cent within 24 months, i.e., only 4 more women in every 100 conceived after 2 years than had conceived after 1 year. The author feels that it is reasonable to investigate infertile couples as soon as a year has passed without pregnancy. The advantages in earlier investigation he stresses are that the sexual drive is greater in the earlier years of marriage, and that non-conception may itself give rise to psychosomatic factors preventing fertility. *Eileen Wilson*

218. **The Fertilizing Capacity of Spermatozoa.**

By R. W. NOYES. *West. J. Surg.*, **61**, 342–349, June 1953. 8 figs. 10 refs.

The author, working at Stanford University, found that when sperms which have been in the uterus of a rat are transferred to the uterus of a postovulatory recipient rat, they are able to fertilize the recipient's ova 2–3 hours sooner than sperms transferred directly from the epididymis to the uterus of a post-ovulatory rat. This supports similar conclusions reached from rabbit experiments that passage of the spermatozoa through the female tract increases their fertilizing capacity.

[The original paper must be consulted for details of the technique used.] *D. C. A. Bevis*

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

219. **Primary Carcinoma of the Vagina : A Report of 46 Cases.**

By M. D. BIVENS, *Amer. J. Obstet. Gynec.*, **65**, 390–399, Feb., 1953. 4 figs. 23 refs.

The youngest patient in this series was 15 years. One had worn a glass pessary for 2½ years without removal and 2 others had senile vaginitis which caused delay in diagnosis. Painless abnormal bleeding, post-coital in 7 cases, was the first sign in 31 (67 per cent). In 8 the first symptom was leucorrhoea, in 3 it was pain in the perineum, 3 felt a nodule in the vagina before noting any symptoms, and 1 80-year-old did not suspect anything wrong till a painful metastatic lesion appeared on her thigh. Thirteen cases were of the everting papillary type, 25 were infiltrating and 3 were of the annular constricting form making the vagina into a narrow rigid tube. In 40 there was clinical extra-vaginal extension; the broad ligaments were infiltrated in 19, recto-vaginal septum in 7, bladder in 5, rectum in 4, inguinal nodes in 3, vulva in 1 and bony ischium in 1. Distant metastasis to bone was proved by X-rays in 4, 1 had pulmonary metastasis, while other terminal cases had metastasis to liver, adrenals, brain and skin. Forty-three cases were squamous cancers and 3 papillary adenocancers. Twenty-eight patients were treated by radium and X-rays, 7 by surgery and radiation, 6 with X-rays only, 4 with radium only, and 1 refused therapy. In the 45 treated cases there were 11 5-year survivals (24.4 per cent).

The author rightly states that progress in therapy is more likely to be made if patients with this rare disease are funneled into the larger treatment centres. *F. J. Browne*

220. **Sub-urethral Fibromyomata in the Female.** (Les fibromes sous-urétraux chez la femme.)

By P. FUNCK-BRETANO, H. ROBERT, and B. GUILLERMO. *Gynéc. Obstét.*, **52**, 12–20, 1953. 25 refs.

Sub-urethral fibromyomata of the vagina only occupy a very small place in the classical writings. It is however necessary to know the symptomatology of these tumours which are generally histologically benign, but which can nevertheless be the cause of serious symptoms, haemorrhage, infection and malignant changes.

As their development is slow, fibromyomas of the vagina remain latent, not infrequently for a long time. It is only after having attained a certain size that symptoms may arise: a feeling of heaviness, less often true pain, discharge, urinary symptoms, or vaginal bleeding.

These tumours can attain the size of an orange or even become larger. They consist of muscular and connective tissue which is very vascular, particularly during pregnancy. Amongst aetiological factors trauma, infection, and nulliparity have all been considered as possibilities.

Early diagnosis is important and the authors advise surgical removal despite the fact that X-rays and radium have given satisfactory results according to some gynaecologists. *D. Maxwell*

221. **Debatable Uterine Tumours.**

By F. A. LANGLEY, J. P. SMITH, and A. S. WOODCOCK. *Acta obstet. gynec. scand.*, **32**, 143–169, 1953. 24 figs. 52 refs.

Writing from the departments of Obstetrics and Gynaecology and of Pathology of Manchester University, the authors describe in detail 4 morphologically dissimilar uterine tumours. Two of them originated in the endometrium; of these, 1 appeared in part carcinomatous and in part sarcomatous; the second was entirely sarcomatous. The third tumour was a case of stromal endometriosis, and the fourth arose in the wall of the uterus and resembled a granulosa-celled tumour.

These cases are taken to illustrate Gruenwald's thesis that the non-epithelial tissues of the utero-vaginal canal arise not only from the mesenchyme originally present in the area but also from the inner and outer linings of the Müllerian ducts, and that Müllerian tissue retains its potentiality for differentiation in the adult. A clear-cut distinction between epithelial and non-epithelial structures may, therefore, not always be possible in tumours of derivatives of the coelomic wall. Embryological evidence is also adduced that uterus and ovary may be derived from the same mesenchymal anlage; thus the occurrence in the uterus of an ovarian type of neoplasm (case 4) should be explained.

While tumours should generally be classified by the

tissue or cell type from which they originate, the embryological approach, employed in the 4 cases described, is a reasonable means of explaining the varying morphology of such baffling neoplasms.

N. Alders

222. **Cancer of the Uterus: The Wertheim Operation.**

By H. H. SCHLINK. *Med. J. Aust.*, **1**, 503–508, Apr. 11th, 1953.

Prior to November 16, 1898, the day on which Wertheim performed his first radical hysterectomy with removal of the lymphatic glands, all women suffering from cancer of the neck of the womb were doomed to die. The immediate mortality has been slowly but consistently reduced to 3.9 per cent. Between the years 1930-1946 at the Royal Prince Alfred Hospital 635 patients were examined with a view to treatment; of these 600 were treated, with a survival rate of 35.3 per cent for five years, and 28.6 per cent for 10 years. Radiotherapy has no effect on cancer cells once they have reached lymphatic glands, and nothing but radical removal can give the patient a chance of a 5- or 10-year cure. In 1930, recognizing that septic malignant ulcers could be rendered aseptic by radiotherapy, the author embarked on the use of pre-operative radiotherapy followed by radical surgery. Schlink now gives one application of 7000 milligramme-hours of radium disposed so that thirty milligrammes with platinum screenage of one millimetre are applied within the uterus, and two corks or moulds of 20 milligrammes of radium with two millimetres of platinum screenage are applied to each of the lateral fornices, all radium being removed in 100 hours. This is followed in 4 to 6 weeks by Wertheim's radical hysterectomy. The operability rate in all cases is 51.4 per cent.

Patients not suitable for operation are treated by radiotherapy which has a primary mortality rate as peritonitis may result. The real test of cure by radiation is found between the fifth and tenth years; and there is a great fall in the cure rate curve of patients treated by radiotherapy alone.

The great danger to the ureter in Wertheim's operation has been stressed, but in nearly 500 Wertheim operations at the Royal Prince Alfred Hospital till 1951 only one ureteral fistula had resulted, and it had healed spontaneously.

The ureter however must be treated with respect. Firstly ureteric catheters should not be inserted to make localization of the ureter easier for the operator. Secondly ureters should be gently detached and not stripped off their filamentous surrounding tissues. As they seem immune to invasion by cancer there is no need to clean them till they hang like two polished cables from the brim of the pelvis to their entrance into the bladder. Thirdly ureters should never be squeezed by forceps, held aside by tapes or retractors or pulled forcibly from their few flimsy attachments to the lateral wall of the pelvis especially at the brim or near the bladder.

Cancer of the corpus should be treated by surgery. At the Royal Prince Alfred Hospital following radium and surgery or surgery alone 68.9 per cent of patients survived 5 years and 51.8 per cent survived 10 years. Including all methods of treatment 54 per cent survived 5 years and 39.7 per cent survived 10 years.

S. Devenish Meares

223. **Operative Treatment of Carcinoma of the Corpus Uteri.**

By E. NORDLANDER. *Acta obstet. gynec. scand.*, **32**, 211–221, 1953. 3 figs. 7 refs.

The records of 484 cases of endometrial carcinoma treated at 3 Stockholm hospitals from the years 1917, 1920 and 1925 respectively up to and including the year 1943 were studied. 159 cases were treated by hysterectomy but in only 133 of these was a diagnosis of primary carcinoma of the uterine body, as defined by Heyman, established. [In 9.8 per cent of these 133 cases histological examination of the specimens removed at operation failed to reveal any evidence of malignancy; the carcinomatous tissue had probably been removed entirely at the curettage preceding hysterectomy.] In 18 cases vaginal hysterectomy was carried out; both appendages were removed in 6 instances, unilateral adnexectomy was done twice, and in 10 patients both appendages were left. In 115 cases hysterectomy was performed by the abdominal route; 9 times it was subtotal; both appendages were excised in 100 of these patients, 9 times they were removed on one side only, and in 6 patients both appendages were left.

These 133 patients were followed up 5 years or longer after operation, except in 1 case which could not be traced. 10 patients died of post-operative complications, corresponding to a primary mortality of 7.6 per cent; it is stressed that this figure would be considerably lower if modern methods of anaesthesia and of pre-operative and post-operative care had been employed.

Out of the remaining 122 patients, 3 died from intercurrent disease, and 7 from recurrence within 5 years of operation, the survival rate being 84.8 per cent.

[Good as these results are, it should be pointed out that these figures refer to a carefully selected proportion of all cases of endometrial carcinoma that were treated. About two-thirds of all patients were treated either by surgery combined with radiotherapy, or by radiotherapy alone, the latter method steadily gaining popularity in Swden.]

N. Alders

224. **Report on 1,236 Cases of Cancer of the Cervix.** (Observations rélatives à 1,236 cas du cancers du col utérin.)

By J. CLOSON, P. DESAIVE, and O. GOSSELIN. *Bull. Féd. Soc., Gynéc. Obstét.*, **5**, 128–136, 1953. 1 fig. 11 refs.

There were 1,236 cases of cervical cancer at the Cancer Centre of the University of Liége between 1st January 1925 and 31st December 1945. They represent

14.6 per cent of the total cases of cancer cared for in this Centre during the same period, and constitute 25.4 per cent—the largest group—of malignant disease of the female sex organs. The average age was 52.

From the histological point of view the writers found: 93.7 per cent were epidermal epitheliomas, 4.5 per cent were adeno-carcinomas, 1.4 per cent were mixed epitheliomas and 0.4 per cent were atypical pseudo-sarcomatous epitheliomas.

When seen first they were thus graded according to the international nomenclature: 365 Stage I, 674 Stage II, 177 Stage III, 20 Stage IV.

Most of the cases were treated with radium, and the rest by complete hysterectomy and deep X-ray therapy.

The results of the 5 years were as follows: 26.9 per cent apparent complete cures, and 4.2 per cent non-active state. 64 per cent died of the disease and 4.9 per cent died from intercurrent or non-related other diseases.

The writers have not found the results of treatment in any significant way dependent on the histological type of the growth. The younger the patient the more guarded should be the prognosis. *D. Maxwell*

225. **Small Preulcerative Invasive Carcinoma of the Cervix: the Spray Carcinoma.**

By W. Schiller, A. F. Daro, H. A. Gollin and N. P. Primiano, *Amer. J. Obstet. Gynec.*, **65** 1088-1098, May 1953. 7 figs. 14 refs.

The earliest recognisable change in squamous epithelioma of the cervix is in a short row of basal cells which assume a carcinomatous character. Like the normal basal cells they undergo mitotic division and are pushed upwards into more superficial strata, but unlike the normal cells they do not undergo differentiation. The presence of large misshapen hyperchromatic nuclei in immature cells lying in a stratum which normally has cornified cells without nuclei supports the diagnosis of carcinoma. Attributes such as "irregular", "polymorphous", "atypical" cannot be defined so precisely that two investigators independent of each other will make the same diagnosis. These terms leave a wide range to individual interpretation and are also used for non-carcinomatous cells. Investigations by the authors show that in the cervix there is no basement membrane in the strict sense of the term, the epithelium being attached to the stroma by pseudopodia-like projections of the cytoplasm of the basal cells so that it is incorrect to speak of the malignant cells "breaking through the basement membrane" when invasion occurs.

While most squamous epitheliomas of the cervix show proliferation of the basal layer towards the surface before invasion, in some this intermediate stage is absent, the transformation of basal cells into carcinoma being followed immediately by downgrowth into the stroma, the higher strata of the squamous epithelium remaining normal. This "carcinomatous invasion in the depth" makes rapid progress. On gross inspection the surface looks normal and gives no clue to the changes in the depth, and they cannot be distinguished by Papanicolaou stain and smear, iodine painting or culdoscopy. This explains some of the false negative smears in early carcinomas. Among these is a sub-group in which there are no strands invading the stroma but the invasion is by single cancer cells which form a brush or spray-like structure. They lose all connection with the neighbouring carcinoma cells and probably develop into carcinomas of especially high malignancy.

Numerous observations have shown that the interval between surface extension and downgrowth in cancer in situ can vary from probably a few days to several years, and there is no correlation between the status at the surface and the extent of the downgrowth. There may be a surface carcinoma several millimetres in diameter with no downgrowth for months or years and, on the other hand, a surface carcinoma of minimal size may have produced a downgrowth larger in volume than the carcinoma at the surface.

[This paper is important and worth careful study. But surely no one thought that every squamous epithelioma of the cervix passed through the stage of a fully developed carcinoma *in situ*; and is not the rapidly invading form described by the authors what has commonly been called "basal cell cancer"?

Probably, as the authors say, it explains some at any rate of the false negative smears in early cervix cancer, for the surface of the cervix is normal and neither the iodine test of Schiller nor the culdoscope will reveal "cancer in depth".] *F. J. Browne*

226. **Radioactive Colloidal Gold in Carcinoma of the Cervix.**

By S. D. Soule, *West. J. Surg.*, **61**, 297–300, June 1953. 6 refs.

The author reviews the present position of this form of therapy used at the Jewish Hospital and Washington University. Au^{198} is a suitable isotype for attacking the lymph nodes distant from the uterus as it is readily phagocytosed, has a half-life of 2.7 days and the greater part of the ionization produced occurs in the area immediately surrounding the source. The colloid is suspended in 1–2 per cent pectin solution to increase viscosity and minimize leakage and absorption into the general circulation. 50-75 millicuries are injected directly into each parametrium, intracavitary radium being used also in most cases. Sixty cases have been treated and 45 subjected to total hysterectomy and pelvic lymphadenectomy. It is too soon to evaluate results but there is evidence that effective radiation of the lymph nodes is produced by the gold. The procedure is safe and reactions to the gold are minimal. The author considers that further work is fully justified. *D. C. A. Bevis*

227. **Value of Serial Biopsies Following Irradiation of Carcinoma of the Cervix.**

By K. A. McGarrity, *Med. J. Aust.*, **1**, 694–698, May 16th, 1953. 2 figs. 6 refs.

The author has followed the work pioneered by Glucksmann and Spear in assessing the radiocurability of carcinoma of the cervix by the study of serial biop-

sies before and after irradiation. Irradiation can be proved by this method to be inadequate in the treatment of patients with carcinoma of the cervix which are radioresistant.

The author shows figures taken from various world centres, which demonstrate the closeness of the figures for the 5- and 10-year cure rate, following treatment by surgery or radium or both. Only in Stage III cases are the figures slightly in favour of irradiation followed by surgery, whereas the Stage I and II figures are very close regardless of treatment used, over both 5- and 10-year periods.

He draws the conclusion that the assessment of radioresistant cases, particularly in Stages I and II, enabling them to be treated by surgery within 6 weeks of the preliminary irradiation, increases materially the salvage rate in carcinoma of the cervix.

S. Devenish Meares

228. **A Twenty Year Study of Radiological Treatment of Cancer of the Cervix at the Montreal General and Royal Victoria Hospital.**

By E. PERCIVAL, *Amer. J. Obstet. Gynec.*, **65**, 386–389, Feb. 1953. 5 refs.

This is a report on 1,200 cases of invasive cancer of the cervix uteri treated between 1927 and 1946. The usual treatment was 2 radium applications at 1-day intervals followed by deep X-rays. The total dose of radium varied from 4,500 to 6,000 mg. hours. Cases complicated by infection were treated by X-rays followed by radium. The results are shown in 2 periods, 1927 to 1936 and 1937 to 1946. In the first series there were 64 Stage I cases out of a total of 557; the 5-year cures in the Stage I cases were 71.4 per cent and the total cure rate in Stage I cases was 73.3 per cent and the total 5-year cure rate 40.4 per cent. Partly explaining the improvement in the results in the second period is the fact that in this period there was a higher incidence of early cases due to the educational work of the Red Cross Society.

The author at present favours radiation rather than surgery in treatment of cervical cancer and anticipates progress from new sources of radiation such as cobalt and gold. She rightly points out that anything less than very radical removal of all the pelvic organs and all the glands will prove worse than useless.

F. J. Browne

229. **Squamous Cell Carcinoma Arising in Benign Cystic Teratoma of the Ovary: a Report of Three Additional Cases and Review of the Literature.**

By R. L. ALZNAUER, *Amer. J. Obstet. Gynec.*, **65**, 1238–1247, June 1953. 6 figs. 17 refs.

Only 60 cases of primary squamous carcinoma arising in a dermoid cyst have been reported, so that including the 3 cases now described the total number of proven cases is 63.

The youngest of the author's 3 cases was 26 years and the oldest 88. The patient usually came complaining of abdominal swelling and lower abdominal pain and on examination there was a mass filling the pelvis and extending to the umbilicus. In 1 of the cases the cystic mass was not adherent and the patient is well 3 years after supravaginal hysterectomy and bilateral salpingo-oöphorectomy. In the other 2 cases bowel and uterus were infiltrated and in 1 of them there was a fistulous opening into the left vaginal fornix. Cell nests were present in 2 of the tumours while in the third there were immature cells without any cell nests.

The author stresses the importance of removing all ovarian cysts (including dermoids) as soon as possible because of the risk of malignant change; in 5 of the reported cases the tumour was known to have been present for 8, 13, 16, 19 and 20 years respectively. All dermoids too should be carefully examined after removal. The mortality of malignant dermoid is very high. In the 32 cases the outcome of which is known it was 87.5 per cent with an average survival time of 5 months following surgery.

F. J. Browne

230. **The Factors Influencing Prognosis in the Treatment of Papillary Cystadenocarcinoma of the Ovary.**

By R. C. BENSON, R. S. SHERMAN and E. L. LUCIA, *West. J. Surg.*, **61**, 387–401, July 1953. 3 figs. 19 refs.

137 cases of the condition are reviewed at the Departments of Gynaecology and Radiology of the University of California Hospital from 1932 to 1952. Only primary ovarian tumours are considered. 128 cases had had cysts for at least 3 years and surgery or surgery and X-rays was the method of treatment used. Ages varied from 22 to 78 and two-thirds of the women were postmenopausal when the diagnosis of malignancy was made; 72 per cent were over 45 at this time. The signs and symptoms were vague and indefinite and 19 cases had postmenopausal bleeding. 40 per cent of the cases were far advanced when first seen. X-ray films of the abdomen were helpful in making the diagnosis as these showed a mass of soft tissue with flecks of calcium in it (psammoma bodies). Paracentesis of the ascites enabled masses to be more easily felt. Staging of the tumour is of crucial importance and Kerr and Elkin's classification is used:

Stage 1: removal of all the primary tumour and visible metastases was possible. Stage 2: ascites with malignant cells was present at operation or partial or total removal of primary was possible but not all visible metastases. Stage 3: recurrence following either operation or irradiation. Stage 4: inoperable tumour, distant metastasis.

This classification is not regarded as ideal as it leaves out such things as adherence of the tumour, bilaterality, etc., but its use is urged. Grading on the degree of differentiation of the cell types was attempted although great variation in different parts of a single tumour was found. Treatment was divided into surgery and surgery with irradiation, this being sub-divided into "arrest" (more than 2000 r in 3-6 weeks) and "palliative" (less than 2000 r).

For the total series the survival rates were 39 per cent over 3 years, 30 per cent at 5 years and 20 per cent

at 10 years. No difference in survival rates was observed in women under 45 and women over 45. The rates were also the same at 3 years in serous cysts and pseudomucinous cysts. Patients in Grades 1 and 2 had a greater chance of survival than those in Grades 3 and 4. The presence of ascites markedly reduced the survival rates. The likelihood of survival decreases with advance of stage and this must be taken into account in comparisons of differing series. Irradiation improves the results compared with surgery alone but is contra-indicated in patients with widespread carcinoma.

In the discussion which followed the presentation of this paper to the Pacific Coast Obstetrical Society, it appeared that increasing the operative rate or completeness of operation did not offer an improved prognosis and the use of radiotherapy in association with surgery was strongly urged. The use of intraperitoneal radioactive gold is also of use in the palliation of ascites, although it did not increase the survival rate in a small series of cases. The only aid to diagnosis in "silent" cases would seem to be more frequent exploratory laparotomy. *D. C. A. Bevis*

231. **So - Called Granulosa- and Theca - Cell Tumours.**

By T. GYLLING. *Gynaecologia, Basle*, **136**, 28–43, July 1953. 7 figs. 61 refs.

Nineteen cases of granulosa cell tumours have been collected by the author. In 9 cases the patient was of reproductive age, while 10 were post-menopausal. The age range was from 30 to 71. Fifteen of the tumours were histologically granulosa cell tumours, 2 being unusually large, and 1 of these was clinically and histologically malignant. Illustrations are given to show the histological character of some of these tumours. In patients of reproductive age varying periods of amenorrhoea with metrorrhagia occurred. Two of these cases only had total amenorhoea. In the post-menopausal group, all had uterine bleeding. Cystic glandular hyperplasia of the endometrium was demonstrated in 16 cases where biopsy was performed. In 1 case there was in addition adenocarcinoma of the endometrium.

Four of the tumours are described as fibrillary and typical of the tumours described as theca cell tumours.

The period of follow-up is so far too short to determine the malignancy of the tumours in the present series. *Josephine Barnes*

232. **Primary Malignancy of the Female Urethra. A Review of Recent Literature and Report of 25 cases.**

By D. W. RITTER, *West. J. Surg.* **61**, 420–429, July 1953. 7 figs. 43 refs.

Carcinoma of the female urethra is more common than early reports would suggest and, as the urethra is involved in many potentially malignant conditions (leukoplakia, caruncles, etc.), every lesion of the urethra should be considered malignant until proved otherwise by microscopic examination. The incidence of malignancy at Los Angeles County Hospital is 1 in 236 admissions to the urological clinics. Most cases occur in the 5th decade and in married parous patients. The commonest symptoms are haematuria, dysuria and the presence of a tumour, but all the common minor disorders of micturition may occur and there is no diagnostic sign or group of symptoms characteristic of the condition. The diagnosis rests on the findings at biopsy. The commonest lesion is a squamous cell carcinoma and this is usually located either in the anterior urethra or the entire urethra. Metastasis occurs early to the inguinal glands and 25-50 per cent of cases have inguinal involvement when first seen. Adenocarcinoma arises from the periurethral glands and is usually found near the meatus. The prognosis in all types is poor but is best in adenocarcinoma (because of late metastasis) and where the lesion is located in the anterior portion of the urethra. As treatment is limited, great emphasis must be placed on prophylaxis and there must be early treatment of all genito-urinary infections and early biopsy of all urethral lesions. So far there have been too few cases treated by radical surgery for a proper evaluation to be made but this seems to offer most for the advanced case; the mortality and morbidity are high however and kidney lesions follow ureteral transplants and the social and sexual activities of the patient are curtailed. Treatment in general is still a matter of controversy; radium does not seem to offer much as squamous carcinoma recurs and adenocarcinoma is radio-resistant. Inguinal block dissection would seem to be indicated in all cases of squamous carcinoma as metastasis occurs so early; the Basset dissection used for carcinoma vulvae is satisfactory and, if this is not done, the inguinal area should be irradiated. Probably the best chance of survival rests on surgical extirpation of both primary and metastatic deposits and pelvic exenteration may be necessary for involvement of the middle or posterior urethra. Radium should be used if the patient is a poor surgical risk and X-rays serve best as an adjunct to surgery or for palliation. Radioactive gold may be useful for inguinal involvement but very few cases have been reported so far.

The author's cases occurred between 1939 and 1951 and one is living 9½ years after treatment but has a vesico-vaginal fistula following intraurethral radium and another is alive after 4 years having had a polyp removed from the posterior urethra. All the other patients are dead or have been followed for less than 3 years.

[This is a good review of the subject and should be read in its entirety.] *D. C. A. Bevis*

233. **Malignant Chorionepithelioma and Chorionic Epithelium.** (Corionepitelioma maligno e corion-epiteliosi.)

By H. HUBER and G. HÖRMANN, *Riv. Ostet Ginec*, **8**, 1–10, Jan. 1953. 2 figs. 4 refs.

The authors review briefly the history of chorionic epitheliomata of the last sixty years. They consider that chorionepithelioma is an extremely malignant

carcinoma of the chorionic villi in which early diagnosis and immediate radical surgical measures, with radiation, have the only hope of achieving successful results. They were surprised that, in reviewing the cases which had occurred in the last 30 years in the Gynaecological Clinic of the University of Kiel, it was found that of 22 cases only 3 had died. Previous authors have reported successful cures of 40–50 per cent of cases and from America a recent claim of 70 per cent cure had been made. The percentage of absolute cure in the Kiel cases of 86 per cent surprised the authors. Of the 22 cases, 13 had malignant proliferation limited to the uterus only and, of these 13, all are claimed as cures of not less than 3 years and 3 of the cases survived more than 12 years. Of the remaining 9 cases, 5 had vaginal metastases and 2 of these survived more than 20 years, 2 more than 10 years, and 1 more than 2 years. The 4 remaining cases all had pulmonary metastases and, of these, 1 was still alive after 3 years.

The treatment of the cases confined to the uterus was, in 12, total hysterectomy and, in 1, application of radium only. Only 1 of the 12 cases of total hysterectomy was given radiotherapy. Of the 5 cases with vaginal metastases, 3 had followed hydatidiform mole, 2 were treated by total hysterectomy and bilateral salpingo-oöphorectomy and one by vaginal hysterectomy and right salpingo-oöphorectomy. The 2 other cases with vaginal metastases followed abortions, 1 of which was treated with total abdominal hysterectomy and bilateral salpingo-oöphorectomy, together with pelvic lymphadenectomy and radiotherapy, the other by curettage, removal of the vaginal metastases, and deep X-ray therapy. This last case is surviving after 21 years. Of the 4 cases of chorionepithelioma with both vaginal and pulmonary metastases, 3 died within 4 months of radical treatment combined with radiotherapy. The 1 remaining case has been observed for 3 years after similar treatment, the pulmonary metastases having regressed spontaneously.

In studying the question of ectopic chorionic tissue, both benign and malignant, the authors conclude that the proliferation of this tissue, both within and without the uterus, is associated in the majority of cases with a maldeveloped zygote, incapable of normal development. There is an atypical function and growth of the chorionic epithelium of these abortive products of conception which possess a tendency to infiltration and of transportation and implantation to distant sites. Heterotopic chorionic epithelium nearly always undergoes spontaneous regression and, in this sense the authors describe it as ectopic chorionic epithelium of uterine or extra-uterine type, drawing an analogy with uterine and extra-uterine endometriosis. Only exceptionally does malignant degeneration occur in the true sense of malignant chorion epithelioma. This definite alteration in the cellular morphology cannot always be ascertained with certainty. The indications for therapy depend upon histological examinations, clinical progress and on repeated quantitative hormone estimations.

The authors believe that it is possible to select a therapy for chorion-epithelioma consisting of radical surgery alone, or surgery combined with intense radiotherapy. Repeated quantitative hormone estimations are important in judging the regression of ectopic chorionic epithelium. In cases where such gonadotrophic hormones persist or reappear after a period of absence, radical operative treatment combined with intense Röntgen therapy is indicated.

Patrick Steptoe

234. **Chorionepithelioma. A Presentation of Case Histories.**

By H. C. STEARNS. *West J. Surg.*, **61**, 368–383, July 1953. 11 figs. 10 refs.

The author presents 10 case histories from the University of Oregon Medical School. Three of the 10 patients died and all were operated upon. Early total hysterectomy must be performed but the ovaries should be left *in situ* unless obviously involved. The author recommends oestrogen therapy, especially if there is metastatic spread. Careful follow-up of all cases (as well as those of hydatidiform mole) is essential and biological tests are of great use although not always dependable. In the discussion which followed this paper at the Pacific Coast Obstetrical Society it appears that these cases occurred over 25 years and that oestrogens alone will not stop metastasis. No experience has been gained on the place of vaginal smears in diagnosis of the condition.

D. C. A. Bevis

235. **The Significance of Friedman's Quantitative Test in the Prognosis of Chorionepithelioma.** (Znaczenie ilosciowych prob biologicznych dla rokowania w przypadkach nabloniaka kosmowkowego.)

By M. KOWALSKI. *Ginek. Polska*, **24**, 59–62, Jan.–Mar. 1953. 6 refs.

The author reports the occurrence of chorionepithelioma which developed in a 22-year-old woman a few weeks after evacuation of the uterus for a hydatid mole. Friedmann's quantitative test of the urine indicated a normal pregnancy. At the same time, the cerebro-spinal fluid was negative. A Wertheim operation was performed, and the patient was well 5 years later.

The author emphasizes the difficulties of prognosis in chorionepithelioma. These he explains by the fact that the body resistance to the activity of the villi varies considerably. On the other hand, one has to take into consideration also the varying degree of activity.

The low level of the gonadotrophin in the urine and the cerebro-spinal fluid points to mild activity and a good prognosis in spite of the histopathological recognition of the malignant process.

S. H. Riterband

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